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Assessing the Feasibility of Epidemiologic Research on DEHP Exposure among Renal Dialysis Patients

JRB Associates, Inc.
McLean, VA

Prepared for

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Ira Marks, Leslie Euinton, George Shreiner, Doroth Wellington, and Pauline Wagner.

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Dialysis patients receive DEHP exposure from two sources, blood stored in PVC blood bags and tubing used in dialysis treatment. The Environmental Protection Agency (EPA) conducted a preliminary investigation into the suitability of using this group for an epidemiologic study because of their documented exposure to DEHP. As part of this assessment, the Health and Human Services (DHHS), End Stage Renal Disease Medical Information System (ESRD MIS) data base was evaluated to determine its usability in the conduct of such a study. The end stage renal disease (ESRD) patient population was found not to constitute a viable population for an epidemiologic investigation to determine the health effects of DEHP exposure. The bases for this conclusion were the complexities of end stage renal disease and the multiple factors involved in the treatment of the disease. In, ...

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ASSESSING THE FEASIBILITY OF EPIDEMIOLOGIC RESEARCH ON DEHP EXPOSURE AMONG RENAL DIALYSIS PATIENTS

Ira Marks, M.P.H.
Leslie Euinton, M.B.Ch.B, D.I.H., F.R.S.H.
George Shreiner, M.D.*
Dorothy Wellington, Ph.D.
Pauline Wagner, M.S.
Allen Sinclair, R.N.
Carole Steele, A.R.T.

JRB ASSOCIATES, INC.
8400 Westpark Drive
McLean, Virginia 22102

*Georgetown University Medical School

PROJECT OFFICER
JANE KELLER

TASK MANAGER
JASON TOTH

HEALTH AND ENVIRONMENTAL
REVIEW DIVISION
OFFICE OF PESTICIDES
AND TOXIC SUBSTANCES
WASHINGTON, D.C.

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ABSTRACT

Di-2-ethylhexylphthalate (DEHP) is a plasticizing agent used in polyvinyl chloride (PVC) to give the polymer its flexibility and softness, and may account for up to 40 percent of the final weight of the PVC product. Although insoluble in water, it is soluble in organic solvents and oils.

A two-year bioassay study performed by the National Cancer Institute found that DEHP produced hepatocellular carcinomas and neoplastic nodules in male and female rats, and adenomas and hepatocellular carcinomas in male and female mice.

One human population receiving relatively high exposures to DEHP is dialysis patients. Dialysis patients receive DEHP exposure from two sources, blood stored in PVC blood bags and tubing used in dialysis treatment. The Environmental Protection Agency (EPA) conducted a preliminary investigation into the suitability of using this group for an epidemiologic study because of their documented exposure to DEHP. As part of this assessment, the Health Care Financing Administration, Department of Health and Human Services (DHHS), End Stage Renal Disease Medical Information System (ESRD MIS) data base was evaluated to determine its usability in the conduct of such a study.

The end stage renal disease (ESRD) patient population was found not to constitute a viable population for an epidemiologic investigation to determine the health effects of DEHP exposure. The bases for this conclusion were the complexities of end stage renal disease and the multiple factors involved in the treatment of the disease. In addition, the ESRD MIS data base was found to lack the completeness, consistency, and accuracy necessary to perform meaningful analyses other than demographic analysis.

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CHAPTER 1

INTRODUCTION

Di-2-ethylhexylphthalate (DEHP) is a phthalate ester prepared from the reaction of pthalic acid with the alcohol, 2-ethyl hexanol. Phthalate esters are primarily used as plasticizing agents in polyvinyl chloride (PVC) to give the polymer its flexibility and softness. These plasticizers may account for up to 40 percent of the final weight of the PVC product. DEHP and its isomer, dioctyl phthalate (DOP), are currently the most widely used plasticizers of this type.

Although DEHP is insoluble in water, it is soluble in organic solvents and oils. Because DEHP is dispersed in the polymer matrix and not chemically bound, it can be easily leached out by solubilizing substances. Human blood plasma is one such substance.

The alkyl phthalate esters have uniform physical characteristics. Generally, they are colorless or lightly colored oily liquids with little, if any, odor; they have relatively high boiling points and low vapor pressures; and they are lipophilic, with negligible solubility in water (Graham 1973). Although these compounds possess molecular dipoles, they do not form strong intermolecular hydrogen bonds (Solomons 1980). As a result, they have lower boiling points and lower water solubilities than acids or alcohols of comparable molecular weight.

DEHP is used in resinous and polymeric coatings for food packaging (CFR 121.2514), in paper and paperboard for contact with aqueous and fatty foods, in closures for sealing gaskets, in beverage cups and linings, in containers for the storage of blood and intravenous solutions, and in intravenous tubing. DEHP is also used in vacuum pumps as an organic pump fluid and as a substitute for polychlorinated biphenyls (PCB) in liquid-filled capacitors. It is also registered with the Environmental Protection Agency (EPA) for use as a miticide in orchards.

Dialkyl phthalates are released into the environment during each major stage of handling: manufacture, transportation/distribution, compounding/processing into products, consumer use of products, and disposal. The materials balance analysis for phthalate esters produced in the United States in 1977 showed that 10 percent of the phthalate esters produced were released to the environment (Arthur D. Little 1979). More specifically, 18,900 kkg of phthalate esters were released to the air and 31,500 kkg of phthalate esters were released to surface water during manufacture, processing, transport, and consumer use of products. In addition, 453,800 kkg of phthalate esters were discarded at the end of products' useful lives: 440,200 kkg to landfills and 13,600 kkg to incinerators. Jorque (1973) and Kotzias (1975) have reported substantial leaching of phthalates from landfills to ground water.

Three sources of consumer exposure to phthalates have been documented. In the first, Tomita (1977) reported increased DEHP and di-butyl-phthalate (DBP) concentrations in blood following the ingestion of foods which were stored or wrapped in plastics or other wrappings containing phthalates. In the second, a series of studies has clearly documented DEHP concentrations in tissues and blood of patients and former patients who were exposed to DEHP during medical treatment. For example, Jaeger and Rubin (1972) reported concentrations ranging from non-detectable to 91.5 (u)g/g in lung tissues obtained at autopsy from 13 patients who died after receiving blood transfusions. Hillman et al. (1975) reported significantly higher DEHP concentrations at autopsy in neonatal heart tissues of 17 infants who had umbilical catheterization alone or with blood products. Other authors (Gibson et al. 1978, Lewis et al. 1978, Rubin et al. 1976) followed the kinetics of disappearance of DEHP after blood transfusions. The studies document that patients are subject to phthalate exposure as a result of leaching from plastic products into the blood.

The third documented source of consumer exposure is through the volatilization of phthalates from plastic materials used in automobiles. While the reliability of the data indicating the airborne concentrations generated is open to question, exposure in an unventilated car may conceivably range upwards to 3 mg/m^3 on hot days.

Poole and Wibberly (1977), Mes and Campbell (Mes et al. 1974, Mes et al. 1976), and Overturf et al. (1979) have reported DEHP and/or DBP concentrations in tissues from humans who had no reported medical or occupational exposure to phthalates. Poole and Wibberly reported mean concentrations of 0.06 ± 0.2 (u)g/g in placentae from 10 women who gave birth to normal babies. Mes and Campbell (Mes et al. 1974) reported concentrations of DBP that ranged from 0 to 1.0 (u)g/g and concentrations of 0.01 to 4.0 (u)g/g in adipose tissue samples taken from accident victims at autopsy. In a later study, Mes and Campbell (Mes et al. 1976) reported that DEHP concentrations in three samples of adipose tissue obtained at autopsy ranged from 0.64 to 1.11 (u)g/g. Overturf et al. (1979) reported DBP and DEHP concentrations in the triglyceride fraction of the kidney cortex and medulla in 4 of 17 kidney samples taken at autopsy. Ono et al. (1975) found serum blood levels of DEHP of 389 ppb in patients dialyzed for six hours and up to 1010 ppb of phthalic acid (metabolite of DEHP) after 5 hours of in vitro dialysis.

Mishkel et al. (1979) analyzed autopsy tissues of seven patients (six of whom had been on long-term dialysis and one who had received a massive blood transfusion) and four controls. The authors stated that adipose tissue of the seven patients contained most of the DEHP (up to 460 (u)g/g tissue, no further data provided); bone marrow, brain, and peripheral nerve tissue showed "moderate accumulation" (up to 100 (u)g/g tissue, no further data provided); and lesser amounts were found in the kidneys, liver, lymph nodes, spleen, heart, and lungs.

An investigation into DEHP exposure was conducted by the National Cancer Institute to determine the toxicity and possible carcinogenicity of di-2-ethylhexyl-phthalate. Preliminary reports presently under review suggest that DEHP may be carcinogenic. The two-year chronic feeding study of this plasticizer found the development of hepatocellular carcinomas and neoplastic nodules in male and female rats, and hepatocellular carcinomas and adenomas in male and female mice.

In concurrence with current research trends, study was needed to substantiate these bioassay findings with epidemiologic investigations of health effects in human population. One population identified for study were patients receiving dialysis for end stage renal disease (ESRD). Reasons for selecting this population included:

- The exceptional risk of exposure to DEHP leached into the blood during dialysis treatment
- A dichotomous distribution of the ESRD population receiving hemodialysis or peritoneal dialysis
- The availability of a large data base maintained by the Department of Health and Human Services, Health Care Financing Administration (HCFA), the End Stage Renal Disease Medical Information System (ESRD MIS)
- Interest in performing epidemiologic research on ESRD patients for effects associated with DEHP.

In response, the Epidemiology Branch of the Office of Toxic Substances, EPA conducted a study to determine the following:

- The feasibility of utilizing renal dialysis patients as a population for investigation of DEHP
- Evaluation of the ESRD MIS as a data base suitable for accessing information required to perform appropriate analyses
- If the above population and data base were found satisfactory, to design a protocol for an epidemiologic study of the effects of DEHP on end stage renal disease patients.

In compliance with this direction, the following activities were conducted:

- Contact and interview with the Branch Chief of ESRD MIS
- Contact with a university consulting group, who had performed preliminary analyses of ESRD MIS data, to obtain information on the manipulation they had performed to correct for inadequacies in the data base
- Review of the natural history of pathologies associated with end stage renal disease

- A site visit of a dialysis treatment center to obtain information on the state-of-the-art in dialysis treatment modalities
- Consultation with nephrologists and epidemiologists at the National Heart, Lung, and Blood Institute, the National Cancer Institute, the Georgetown University Medical School Nephrology Department, the University of Texas School of Public Health, and the University of Minnesota School of Public Health.

The information gained from these activities and discussed in chapter 2 suggests that ESRD patients are not a satisfactory population for an epidemiologic study of the effect of di-2-ethylheyxl-phthalate. The basis of this conclusion is the multifactorial aspects of this patient population which include the broad array of pathologies leading to and associated with ESRD, as well as the effects of the different treatment modalities and their corresponding components. Chapter 2 begins with a discussion of contributory components of end stage renal disease, the pathologic process, and the effects of ESRD on the constitution of the body. The second section discusses the three dialysis modalities used in treating ESRD patients. Each modality is described in terms of the process involved, the components of each, the effects attributed to each of these components, and the criteria for selection of one modality over another.

Chapter 3 describes toxicological factors in renal dialysis patients resulting from DEHP exposure. These factors could conceivably produce toxic effects in the ESRD population which may not be representative of those seen in normal animals and humans. The non-unique toxic effects of DEHP make it unlikely that DEHP could be identified as either a primary or synergistic cause of toxic symptoms in dialysis patients. In addition, the generally poor health of dialysis patients, the multiplicity of their drug therapies and their inadvertent exposures to both chemicals and disease because of dialysis could disguise or act syngeristically with DEHP to produce toxic effects.

Chapter 4 concludes that the End Stage Renal Disease Medical Information System (ESRD MIS) lacks the accuracy, consistency, and completeness necessary to perform any meaningful analyses other than demographic. The conclusion is based upon input provided by the Health Care Finance Administration (HCFA) End Stage Renal Disease Medical Information System (ESRD MIS) Branch and the Environmental Epidemiology Branch of the National Cancer Institute. This information is presented in Sections 4.1, "An Overview of the ESRD MIS," and 4.2, "An Assessment of the Epidemiologic Research Potential of ESRD, MIS Data.

Chapter 5 uses a biostatistical approach to discuss the criteria required to derive inferences from an epidemiologic study, i.e., the type and quality of the information which is necessary to determine causal association between exposure to a factor and development of a specific disease outcome. The discussion concludes that ESRD patients would not constitute a viable study group for an epidemiologic investigation of the carcinogenic effect of exposure to DEHP for two reasons: 1) the inability to measure exposure to DEHP separately from exposure to carcinogens and possible etiologic factors; and 2) the extremely high, combined, competitive risk of mortality or morbidity from causes other than primary cancer of the liver or other malignancies.

CHAPTER 2

END STAGE RENAL DISEASE: PATHOLOGIES, TREATMENTS, AND PATIENT POPULATION

L. Euinton, M.B.Ch.B., D.I.H., F.R.S.H.,
G. Schreiner, M.D., A. Sinclair, R.N., and
I. Marks, M.P.H.

"End stage renal disease" is an aggregate term representing a complex cluster of systemic, pathological processes, with additional contributory and associated conditions. This chapter reviews the systemic complexity of end stage renal disease and the problems of multiple exposures associated with the modalities of dialysis.

2.1 THE PATHOLOGICAL PROCESSES OF END STAGE RENAL DISEASE

End stage renal disease, commonly called chronic renal failure (CRF), may occur as a result of many pathological conditions. Each of these conditions has its own group of associated pathologies. The major classes of macropathology include: a) vascular diseases; b) primary glomerular diseases; c) primary tubulointerstitial nephritis; and d) miscellaneous causes, including stones, tumors, cysts, and infiltrative diseases. In addition, there are clusters of uremic symptoms which are common to a given level of renal failure which may be experienced regardless and distinct from the pathology of the underlying kidney disease. The time, course, and specific morphologic changes, as well as the stages, of these pathological conditions are highly variable from patient to patient. As a result, ESRD patients should not be described as a uniform population, even if controlled by sex and age.

Renal failure develops when disease or trauma compromises the ability of the kidney to remove toxic materials from the blood, and maintain fluid, electrolyte, and acid-base balances. The condition may be acute or chronic. Acute renal failure is caused by processes extending over days or weeks and potentially results in recovery from uremia. Chronic renal failure occurs from processes extending over weeks or months, is usually characterized by progression, and exhibits a high degree of variability in the slope or rate of progression. Rapidly progressive disease may evolve from health to renal failure in one to three years, while slowly progressive disease may extend over 30 to 40 years. For functional purposes, it is clinically useful to divide patients into three phases:

- Phase 1, from 100 percent glomerular filtration rate to 20 percent of normal
- Phase 2, from 20 percent of normal to 5 percent of normal
- Phase 3, less than 5 percent of normal.

It is largely the patients in Phase 3 who have been designated by the Government as exhibiting end stage renal disease.

The characteristics associated with chronic renal failure are: nitrogen retention; screened by elevations of serum urea, creatinine, acidosis; screened by pH and depression of serum bicarbonate, anemia; screened by HCT and hemoglobin depression, hyperphosphatemia and hypocalcemia except in hyperparathyroid or other hypercalcemic etiologies; and other electrolyte disturbances, including normal or reduced sodium, normal or elevated serum potassium.

Urinary volume is often relatively fixed between one and four liters per day, and does not respond to variations in water intake. One practical and clinical definition of renal failure is when the daily urine output is the maximum urine output. Urinary osmolarity is usually fixed close to that of plasma (300 to 320 mOsm/l). The findings on urinalysis depend on the nature of the underlying disease, but broad (especially waxy) casts are often prominent in advanced renal insufficiency of any cause. The hematologic picture is that of a normochromic, normocytic anemia of moderate severity.

The outcome of urinalysis depends on the nature of the underlying disorder and superimposed complications. Progression of underlying chronic renal disease is generally not susceptible to specific treatment, although slowing of the rate of progression may be a practical goal in certain diseases. Oliguria, progressive hyperkalemia, and pericarditis are often manifestations of a preterminal state. Even in these situations, however, dialysis and transplantation may improve the outlook.

A renal injury occurs in patients with immune complex deposition where the antigen is endogenous, as in systemic lupus erythematosus (SLE) and neoplasia associated with glomerular disease, but may be exogenous in the case of serum sickness, bacterial, viral, and protozoa-associated glomerular nephritides. Disease from antibodies to glomerular basement membrane glycoprotein occurs in the nephritides of antilymphocyte serum treatment, Goodpasture's Syndrome, and some rapidly progressive forms of idiopathic cresentic glomerular nephritis. Antibodies to other active glomerular antigens occurs in some forms of membranous glomerulopathy and antibody to planted glomerular antigens occurs in SLE, drugs, and post-streptococcal glomerulonephritis. Inflammatory vasculitis involving the glomerulus may occur in periarteritis nodosa, Wegner's granulomatosis, and other vasculitidies.

2.1.1 Some Primary Causes of ESRD

The purpose of this section is to distinguish some of the different causes of kidney disease which may progress to end stage renal disease, or CRF. The pathological process is incited at the glomeruli, at the tubulointerstitial areas, or in the renal arteries, according to the etiology. By the time the stage of chronic renal failure is reached, all of these three sites are involved to some degree. The signs, symptoms, or laboratory tests which may distinguish these conditions by diagnosis are not detailed. But, plainly, the clinical and biological parameters will vary at the stage of CRF according to the etiology and pathophysiology of the renal disease. These parameters may be further complicated by the effect of the disease on other organs, and still further complicated in those patients whose renal involvement is secondary to systemic disease.

Chronic Tubulointerstitial Nephropathy

Chronic tubulointerstitial nephropathy (TIN) includes all those chronic kidney disorders in which generalized or local changes in the tubulointerstitial area predominate over glomerular or vascular lesions. Since some tubulointerstitial changes are associated with all renal diseases, this distinction may be difficult to identify.

Other conditions associated with TIN include:

- Effects related to the use of certain drugs, including analgesics; sulfonamides, penicillin, methicillin, and their homologs; diuretics such as furosemide, thiazide, phenytoin (dilantin), etc.
- Effects related to heavy metal toxins, including lead, cadmium, uranium, copper, mercury, bismuth, thallium, arsenic, and iron.
- Oxalate deposition from ethylene glycol, methoxyflurane, and anesthetic agents, primary hereditary oxaluria and small bowel disease.
- Uric acid nephropathy from gout and hematologic disorders, especially primary and secondary hyperparathyroidism, milk alkali syndrome, sarcoid, neoplasia and multiple myeloma.
- Effects related to malignancy, in which renal interstitial spaces may be invaded by proliferative malignant cells in leukemia and lymphosarcoma. The cortex is involved more than the medulla (Merck et al. 1977).

Chronic tubulointerstitial renal disease is due to ascending bacterial infection. Obstructive uropathy, such as strictures, stones, reflux, myoneurogenic disease, etc., is usually present. Even with advanced disease, proteinuria is usually < 1 gm/sq m/day. The urinary sediments tend to be scanty, but renal epithelial cells, granular casts, and occasionally white blood cell casts are found, especially in analgesic nephropathy (Willis et al. 1972).

The functional features differentiating tubulointerstitial nephritis are: proteinuria less than 2 gm, scant urinary sediment, sodium wasting, and anemia which is disproportionately severe to the level of nitrogen retention; a lesser degree of hypertension, hyperchloremic acidosis, and markedly elevated uric acid for the degree of nitrogen retention; and increased urine volume with decreased maximum osmotic U/P ratio (concentrating ability is one of the most sensitive early signs).

Hereditary Renal Disease

In polycystic renal diseases, the bilateral cysts cause enlargement of the total renal size, while reducing, by compression, the functioning renal tissue. Chronic infection frequently is superimposed and contributes to the progressive loss of renal function. There is also a high associated incidence of intracranial aneurysm, and hypertension is common. Death is usually due to uremia or the complications of hypertensive cardiovascular disease. About 10 percent of patients die of intracranial hemorrhage from rupture of aneurysms.

Polycystic patients make particularly favorable chronic dialysis patients with a five year survival in the range of 80 percent. They tend to have less anemia than other patients with chronic renal disease and lower blood pressures.

Medullary cystic disease, sometimes called juvenile nephronothisis, is a diffuse nephropathy, either genetic or congenital in origin. Retarded growth and evidence of bone disease are common in children. These patients have anemia out of proportion to their degree of renal insufficiency.

Medullary sponge kidney is a tubular ectasia or dysplasia resulting in congenital cystic dilation of the collecting tubules, leading to urinary stasis and nephrocalcinosis. People with this condition often develop infections and can soon develop mild renal insufficiency.

Hereditary nephritis is a familial disorder characterized by hematuria, renal functional impairment, nerve deafness and, on occasion, ocular abnormalities (Merck *et al*. 1977).

2.1.2 Diseases Commonly Associated with ESRD

Auto-immune collagen vascular diseases which involve the kidney include generalized lupus erythematosus (GLE) and polyarteritis nodosa (PAN). Generalized lupus erythematosus clinically shows a variable combination of fever, an erythematous rash (especially of the face), arthritis, pleurisy, enlarged lymph glands and spleen, albuminuria and hematuria, signs of endocarditis and anemia. An important diagnostic laboratory finding is the presence of "lupus-cells" (LE cells) in the blood and bone marrow. These are polymorphonuclear lymphocytes containing rounded masses of phagocytosed altered desoxyribonucleic acid, essentially similar to the haematoxylin-staining bodies seen in the kidneys and other organs. The blood serum often contains excessive gamma globulin and special serological studies give evidence of complex auto-immunity changes, with the formation of antibodies against the patient's own nucleoproteins, anti-DNA, and so injuring the cells of many organs.

Polyarteritis nodosa is a rare febrile illness, probably allergic in nature, with diffuse or nodular acute inflammation of many arteries, chiefly medium-sized and small arteries especially in the viscera. The vessel walls show areas of necrosis, fibrinous exudate, accumulation of neutrophil and eosinophil polymorphonuclear leucocytes, plasma cells, lymphocytes and macrophages. Some arteries show multiple small aneurysms, with multiple small infarcts in the organs, and later organization of the thrombi. Veins adjacent to the inflamed arteries show phlebitis. According to the main distribution of the lesions, the symptoms are highly varied. They may be predominantly alimentary, cardiac, cerebral, muscular, or renal. The disease is often fatal, from emaciation, anemia, hemorrhages, and infarction of the heart, brain, or other organs, but spontaneous recovery sometimes occurs. Steroids are useful in some cases of vasculitis, and cytoxan is specially effective in the subgroup known as Wegner's Granulomatosis (Willis et al. 1972).

In several other diseases, there is strong evidence that sensitization of the tissues to bacterial or other antigenic substances plays an important part. Because all show prominent lesions in connective tissue, including "fibrinoid" degeneration or necrosis, they have been spoken of collectively and vaguely as the "collagen diseases"--including GLE, PAN, and such rare, possibly kidney-affecting diseases as scleroderma and dermatomyositis (Willis et al. 1972).

In addition, two metabolic disease are commonly associated with end stage renal disease:

- Diabetes Mellitus: The complications of untreated diabetes include ketosis, resulting from impaired fat metabolism; hypercholesterolemia and xanthomatosis; arterial atheroma with consequent thrombosis and gangrene of the limbs; diabetic retinitis, which also is secondary to changes in retinal arteries; increased susceptibility to infections, i.e., tuberculosis, and certain renal complications, i.e., glomerular sclerosis of Kimmelstiel and Wilson; and medullary necrosis, especially of the papillae (Willis et al. 1972). Diabetic nephropathy, its pathogenesis, histopathology, and clinical course, was described by D'Elia et al. (1974) from a study of 49 patients of whom 27 percent were blind.

- Amyloid Degeneration: It is probable that in amyloid disease the connective tissue protein, perhaps collagen and elastin as well as chondromucoid, undergoes direct conversion into amyloid, of which, however, there is also a great accumulation causing enlargement of the affected organs. The generalized disease usually results from a longstanding bacterial infection, most often chronic supperative infections, tuberculosis, rheumatoid arthritis, hereditary syphilis, various types of neoplasms including Hodgkin's disease, multiple myeloma and chronic infective endocarditis. A peculiar form of amyloidosis is present in occasional cases of plasma-cell myelomatosis. In the kidneys, deposits occur in the glomeruli, and also around the tubules and in the walls of the larger vessels (Willis et al. 1972).

2.1.3 Conditions Associated with ESRD

The pathology of ESRD includes a number of conditions which inhibit the normal function of various systems within the body. The following is a discussion of three of these conditions, hypertension, uremia, and immunosuppression, and their associated effects.

Hypertension

During the chronic stage of CRF, there is a progressive rise of blood pressure. In malignant cases of essential hypertension, the progressive renal damage and azotemia are secondary to rapidly mounting blood pressure. The renal changes generally resemble those of nephrosclerosis but with severe and characteristic lesions of the arteries, namely a peculiar swelling or fibrinoid necrosis of the walls of the arterioles (especially the afferent glomerular arteries), and a cellular fibrous endarteritis of the larger interlobular arteries. Of special interest are the vascular lesions which are not confined to the kidneys, but occur in the arterioles of many other tissues. This fact suggests that malignant hypertension is a primary vascular lesion with widespread lesions in the arterial system and serious secondary ischemic effects on the kidneys.

Thus, renal ischemia leads to hypertension through stimulation of reninangiotensin resulting in the production of Angiotensin II, a potent vasoconstrictor produced in the body. Ischemia may be the result of a host of obstructive diseases of arteries, including:

- Arteritis, embracing all five inflammations of arteries
- Atheroma or atherosclerosis, a degenerative change in the intima
- Medial calcification or Monckeburg's sclerosis, a degenerative change in the media
- Hypertensive sclerosis, a generalized arterial disease associated with high blood pressure
- Mechanical constriction of arteries
- Local arterial spasm including fibromuscular dysplasia
- Arterial embolism (Willis et al. 1972).

Uremia

Renal insufficiency is a measurable decline in kidney function. Renal failure is a sufficient degree of decline to induce biochemical abnormalities in the serum and loss of the kidney's homeostatic function. Uremia is reached when renal failure becomes symptomatic.

The first manifestations of uremia may be lassitude, fatigue, and often decreased mental acuity. Neuromuscular features include coarse muscular twitches, peripheral neuropathies with sensory and motor phenomena, muscle cramps, and convulsions (usually the result of hypertensive encephalopathy). Gastrointestinal manifestations, such as anorexia, nausea, vomiting, stomatitis, an unpleasant taste in the mouth, are almost uniformly present. Malnutrition leading to generalized tissue-wasting is a prominent feature of chronic uremia. The skin may develop a yellow-brown discoloration, and occasionally urea from sweat may crystallize on the skin as uremic frost. Pruritis is an especially uncomfortable feature in some patients. Hypertension is often present, as are signs of congestive heart failure (Merck et al. 1977).

Uremia has been repeatedly shown to be immunosuppressive according to Matas et al. (1975) and Birkeland (1976), who also confirms that there is an increased incidence of cancer in uremic patients. The mode of connection between these established factors is being pursued.

Immunosuppression

The kidney is frequently injured by those disorders in which the immune system produces antibodies to an endogenous antigen. Several mechanisms for developing an immune response to autoantigens are recognized. Genetic factors play a part. Immunosuppressive agents have been developed which suppress all immunologic reactions and the metabolism of rapidly dividing cells. For this reason, overwhelming infection is the leading cause of death in transplant recipients. Nevertheless, carefully selected and administered immunosuppressive treatment has been primarily responsible for the present success of clinical transplantation.

Evidence for the occurrence of immune responses to a variety of human tumors is increasing. Tumor-specific (or tumor-associated) transplantation antigens have been demonstrated in most experimental animal tumors and in several human neoplasms. It seems likely that the presence of these surface markers on neoplastic cells would allow their recognition by immunocompetent host cells as well as their reaction with antibodies directed against immunogenic surface configurations. The significance of such recognitions and reactions in the pathogenesis and conduct of tumors is currently the object of intensive laboratory and clinical investigations (Merck et al. 1977).

2.1.4 The Complicated Picture of ESRD Patients

The interaction of the pathologies described above has additional effects on the body which contribute to the further deterioration of the overall body systems. Thus, apart from the clinical and biologic parameters affected by the ESRD-induced uremia, patients may suffer a very wide range of symptoms, signs, and complications from the underlying disease process which, to some extent, has either caused or contributed to the failure of kidney function. Thus, hypertension leads to cardiac hypertrophy, then congestive heart failure, and a strikingly increased risk for cerebral vascular accident and myocardial infarction.

The obstructive diseases of arteries, whether associated with hypertension or not, may impair the glomerular and/or tubulointerstitial function of the kidneys, while having ischemic effects elsewhere, i.e., coronary atheroma, diabetic gangrene of limbs, retinal exudates and papilledema, etc.

Kidneys damaged by toxic agents may be accompanied by toxic effects elsewhere, such as the anemia of chronic lead poisoning, and liver damage from any of many toxic agents.

Anemia is seen with uremia, regardless of the underlying renal disease. Unlike the anemia of other chronic disorders, however, decreased body iron stores are not a consistent feature. The anemia associated with ESRD-induced uremia is characterized by a shortened red blood cell survival and diminished erythropoietin production with a subnormal marrow response. In the very rare patient, renal arteriolar microvascular disease may be associated with hypertension, marked hemolysis, and increased reticulocyte production. This so-called hemolytic-uremic syndrome is generally associated with widespread platelet consumption and occlusion of the microvasculature, and convincingly demonstrates a dissociation between renal excretory and endocrine functions (that is, decreased glomerular filtration, but with increased erythropoietin and renin production). The mechanism of the anemia of ESRD, or CRF, is discussed in detail by Fisher (1980).

Spontaneous regressions of human neoplasms have encouraged interest in the immunologic therapy for neoplastic diseases. Present immunotherapy in human neoplasia is based on recent advances in knowledge of humoral and cellular immunity, immunosuppression, human transplantation antigens, and immunologic tolerance, a state in which a substance normally capable of inducing an immune response fails to do so (Merck et al. 1977).

Cancer developing after renal transplantation is a well-documented event that has clinical importance and immunologic implications. Montie (1977) suggests that recent data do not support that cancer after a transplant is caused by suppression of the immune surveillance system. According to Penn (1972), the renal transplant patient has approximately 30 to 100 times greater risk of developing cancer than otherwise apparently similar individuals in the general population. This increased incidence is not reflected in a uniform increase in the incidence of all types of cancers, but is evident primarily in two areas: 1) epithelial tumors of the skin, lip, and cervix account for 47 percent; and 2) solid lymphomas account for 23 percent. The lymphomatous tumors in transplant patients have an unusual predilection for central nervous system involvement and a poor response rate to therapy.

Further data supporting the likelihood that a patient with ESRD is more prone to develop cancer than a patient without renal disease, and that those with glomerulonephritis or phenacetin nephropathy are particularly prone, were provided by Sutherland et al. (1977). However, data pertaining to increased cancer risk in nontransplanted patients are not this definitive, and this is an area in need of further investigation.

2.1.5 Course and Prognosis of ESRD Patients

Dialysis patients have an average survival time of seven to 10 years after the onset of end stage renal disease, or CRF.* An average cross sectional group of dialysis patients will have an average annual mortality of 10 percent. This tends to increase with the mean age of the patient group. During this time, the course and prognosis of ESRD patients varies enormously according to the:

- Nature of the renal disease, and the stage and possibly the duration of the uremic state
- Nature and extent, possibly modified by treatment, of generalized disease or specific organ disease, and the complications which may arise from these
- Immunosuppressive effects of uremia itself or of immunosuppressive drugs administered to the patient

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*An interview with Nancy Blackburn, R.N., and Raphael J. Osweroff, M.D., of the Dialysis Center of Northern Virginia, January 20, 1981.

- High risk of malignancies, some 30 to 100 times that in the general population, known to exist in ESRD patients
- Increasing age of the cohort
- The prevalence of epidemic infections, such as hepatitis and the opportunity for opportunistic infections in suppressed patients
- Further complications in dialysis patients of the dialysis, itself, and the concominant treatment.

2.2 RENAL DIALYSIS

Renal dialysis is the process in which an artificial mechanism is utilized to accomplish the biological cleansing functions normally done by the kidney. There are three treatment modalities used in treating end stage renal disease, or chronic renal failure. They are:

- Hemodialysis
- Peritoneal dialysis
- Continuous ambulatory peritoneal dialysis (CAPD).

Each of these modalities differ in the equipment utilized, the complications associated with each, and the conditions which warrant the use of one over another. At present, the most widely used modality is hemodialysis. However, the criteria used for the selection of one modality over another involve a number of factors, both medical and psycho-social in nature. Some of these are listed in table 2-1.

2.2.1 Hemodialysis

Patients receiving chronic (ESRD) maintenance hemodialysis require four- to eight-hour treatments three times a week to maintain a state of well-being. The hemodialysis process reduces the BUN and creatinine by approximately 50 percent, and corrects metabolic acidosis and hyperkalemia. These patients are also advised to restrict their fluid intake to 1,000 cc's per 24 hours and are usually placed on a special low-protein diet. It has been reported that ESRD patients gain a variable amount of weight per 24 hours between treatments,

CRITERIA	Hemodialysis	Peritoneal	CAPD
Physical competency			x
Intellectual competency			x
Mental retention			x
Reliability			x
Socio-economic level			x
Arteriovenous shunt competency	x		
Arteriovenous graft competency	x		
Patient choice			x
Psychological stability			x
Hyperkalemia, acute life threatening	x		
Acute renal failure with recovery potentials		x	
Lack of sophisticated equipment		x	
Age			x
Motivation			x
Home support	x		x
Cooperation	x		x
Cardiovascular system competency			x
Small children		x	
Older patients (60 years or older)		x	
Home dialysis for patients living alone		x	
Patients refusing blood transfusions		x	x
Holding for transplantation and fistula maturation		x	

TABLE 2-1. CRITERIA FOR SELECTION OF DIALYSIS MODALITY

depending upon their urine output and their level of fluid intake. Hemodialysis may be accomplished in the hospital, in an out-patient clinical setting, or even at home (Guyton 1956).

Hemodialysis involves a mechanical "kidney machine" consisting of three essential components:

- The exchanger, a membrane unit where the body's blood, carrying the waste and toxic materials of the body, comes into direct contact with the infused fluid (dialysate), its purpose being to take on the body's waste and toxic materials, thereby cleansing the blood
- A tubing system utilized for the conduct of the patient's blood and dialysate to and from the membrane component
- A dialysate delivery system, comprised of the machine itself and dialysate, composed of a buffering component, usually acetate or bicarbonate, with electrolytes and glucose.

Each of these components has the potential of exposing the patient to contaminants, producing adverse iatrogenic reactions (table 2-2).

Membrane Unit

Hemodialysis units basically fall into three fundamental categories, based on the type of membrane used in the unit. These three categories are:

- Parallel plate or sandwich design
- Coil
- Hollow-fiber devices.

The underlying purpose of these membranes is to provide an influencing factor on the transport of solutes from the blood to the dialysate. The successful function of the particular membrane will assist the clinical team in maintaining the patient in metabolic homeostasis.

Each membrane has certain mechanical differences which influence the physiological dialyzing of a patient. Some of these characteristics are highlighted in the following paragraphs.

COMPLICATION	Hemodialysis	Peritoneal	CAPD
Peritonitis		x	x
Tunnel infection		x	x
Hernia		x	x
Anemia	x		
Electrolyte inbalance	x	x	x
Weight	x	x	x
Low back pain		x	x
Cramps, abdominal and extremities	x	x	x
Shoulder pain		x	x
Chest pain	x		
Cardiac arythmia	x		
Excessive fluid loss		x	x
Fluid overload			x
Blood tinged drainage		x	x
Congestive heart failure	x	x	x
Osteodystrophy	x	x	x
Hypertension	x	x	x
Hydrothorax		x	x
Atelectasis		x	x
Protein loss		x	x
Hyperosmolar coma		x	x
Hypernatremia		x	x
Hypotension	x	x	x
Hemorrhage	x	x	x
Hypokalemia	x		
Air embolism	x		
Pyrogenic reactions	x		
Hemolysis	x		
Seizures	x		
Thrombosis	x		
Hepatitis	x		
Neuropathy	x	x	x
Hyperuricemia	x	x	x
Constipation	x	x	x
Menstrual dysfunction	x	x	x
Infertility	x	x	x
Sexual problems	x	x	x
Insomnia	x	x	x
Dialysis dementia	x	x	x
Sclerota peritoneum		x	x
Leukopenia	x		
Dermatitis	x		
Arteriosclerosis	x	x	x
Encephalopathy	x	x	x

TABLE 2-2. POTENTIAL COMPLICATIONS PER MODALITY

COMPLICATION	Hemodialysis	Peritoneal	CAPD
Osteomalisia	x	x	x
Hypercalcemia	x	x	x
Anorexia	x	x	x
Gastroenteritis	x	x	x
Pulmonary edema	x	x	x
Cardiac atheroma	x	x	x
Myocardial infarction	x	x	x
Cerebral thrombosis	x	x	x
Intracranial hemorrhage	x	x	x
Cardiac tamponode	x	x	x
Sepsis	x	x	x
Lymphoma, non-Hodgkins	x	x	x
Death	x	x	x

TABLE 2-2. POTENTIAL COMPLICATIONS PER MODALITY (continued)

Plate or sandwich design dialyzers consist of parallel sheets of cellophane sealed at the edges between grooved polypropylene membrane supports. Blood passes one way between the sheets, while dialysate passes in the opposite direction outside of the membranes. The arterial-venous pressure gradient is sufficient to circulate the blood through the membranes without a pump (Hampers et al. 1973). Ultrafiltration is the removal of solute-containing fluid by means of a transmembrane pressure differential. This may be accomplished either by raising the internal hydrostatic pressure of the blood or applying a negative pressure to the dialysate compartment. In practice, usually both are used and the ultrafiltration pressure gradient becomes the sum of the positive and negative pressure.

In coil dialyzers, tight concentric coils of cellophane tubing are separated by screening or mesh spacers. Blood is pumped through the inside of the tubing, and dialysate circulates through the coil outside. Ultrafiltration is accomplished by partially obstructing the outflow of blood from the coil with a screw clamp, thus increasing the blood pressure within the coil (Hampers et al. 1973).

Hollow-fiber dialyzers consist of a bundle of hollow cellulose fibers 200mm in diameter through which the blood passes. Dialysate is circulated around the outside of these fibers in a countercurrent fashion. This dialyzer is compact and efficient because of the high ratio of surface area to blood volume. Like the parallel sheet dialyzer, blood flow resistance is low.

The membrane unit is a potential medium for introducing factors that may result in an adverse patient reaction. Mechanical trauma imposed on the red cell by the artificial kidney itself results in considerable loss of membrane lipoid and premature red-cell senescence (Kjellstrand 1978).

Studies have shown Beta thromboglobulin (BTG) levels significantly elevated in patients on chronic hemodialysis. Beta thromboglobulin, a platelet-specific protein, can be utilized to determine the clinical stability of the platelets whose integrity are essential to the clotting mechanism. It is not liberated from the platelet during exposure to heparin, but is liberated during the release reaction coming in uremia. So, the increased BTG levels are not due to turbulent flow within the vascular access, but may be due to platelet aggregation within the hemodialyzer during the first hour of dialysis. This effect is observed with the Travenol CF series hollow fiber (cuprophane) equipment, but not with the Cordis-Dow artificial kidney (regenerated cellulose) (Adler et al. 1979).

Dialyzers with cellulose membranes were found to cause marked leukopenia in a study conducted by J. Shin, while its occurrence was significantly less in non-cellulose membrane dialyzers. The extent of white blood cell decrease seemed to correlate inversely with an increase in the ultrafiltration rate per membrane area of dialyzer. However, there are recent reports that indicate that leukopenia and hypoxia are possible unrelated effects of hemodialysis (Shin 1978).

In recent years, there has been a discussion of the reuse of membranes and the effect on the hemodialyzed patient. Membranes are intended for single use, so reused membranes lack the protection from contamination originally provided by the manufacturer (Hampers et al. 1973).

Because there is no definite policy on the reuse of membranes, it is difficult to ascertain the number of patients being dialyzed with reused membranes. At the same time, it would be difficult not to ascribe certain clinical manifestations to the reuse of dialyzers (Anonymous 1980). Thus far, reductions in dialyzer efficiency and adverse patient reactions, including fever and infection, have been demonstrated following reuse. In addition, the practice of storing dialyzers filled with diluted formaldehyde can result in an increased number of patient reactions to formaldehyde (Willingmyre 1979).

"Agents used to sterilize dialyzers, to reduce bacterial counts in the fluid pathways of artificial kidney machine, water treatment, and water or dialysate distribution systems have included sodium hypochlorite, chlorine dioxide, benzelkonium chloride, 27 percent sodium chloride, and formaldehyde" (Kjellstrand 1978). These compounds have been associated with various clinical manifestations of hemolysis, hepatitis, fever, and even death.

Reported adverse effects from the reuse of dialyzers can be categorized into the following areas:

- Increased risk of infections from improperly sterilized membranes
- Pyrogenic or hemolytic reactions from the residues of sterilants and other substances such as formaldehyde
- Deterioration of dialyzer performance parameters
- Immunological reactions resulting from formaldehyde-residual blood interactions (Anonymous 1980).

Significant residuals of formaldehyde and toxic reaction products of ethylene glycol were identified in the flood compartment of the dialyzer after proper preparation for dialysis and untoward patient reactions were attributed to these residues (Willingmyre 1979). However, the synergistic reaction of these residues and products on the various multitudes of oral, intravenous, and intramuscular medications received by the patient might also result in unexpected, untoward clinical manifestations. Some positive benefits to reusing a dialyzer include less blood loss, and probably less activation of complement, which may be one of the factors associated with the production of leukopenia during the first hour of dialysis.

Tubing System

The dialysis access and extracorporeal blood components include:

- Arteriovenous shunts for access to the patient's blood systems
- Tubing for transporting blood from the filtration membrane back to the patient.

Access to the circulation for hemodialysis is generally obtained with an arteriovenous (AV) shunt or fistula. An arteriovenous shunt consists of Teflon vessel tips inserted into the radial artery and cephalic vein (or other accessible vessels in an upper or lower extremity). These vessel tips are linked by a silicone rubber cannula or tube external to the skin. Two sections of the cannula are joined by a connecting piece of Teflon and are separated at the connector for dialysis. After each dialysis session, the cannula loop is rejoined with a new Teflon connector.

Subcutaneous arteriovenous fistulas avoid the recurrent infections and clots associated with shunts. They permit a freer lifestyle for bathing and swimming, and have largely replaced the arteriovenous shunts for vascular access. The radial artery is anastomosed to the cephalic vein in an end-to-end, end-to-side, or side-to-side fashion. The forearm veins dilate, eventually arterialize, and are suitable for repeated puncture which may be used with a single needle alternating pump device or two needles placed in the opposite directions within the flowing stream, the proximal needle being used for intake and the venous needle for outflow (Morgan 1973). Plastic tubing is utilized as the pathway to transport the blood between the exchange membranes, the machine, and the patient.

Plastic tubing contaminants, such as plasticizers, have been implicated as causing severe and complex reactions. Plastics used in the dialysis procedure contain unreacted materials capable of being leached from the plastic when in contact with lipotrophic components of the blood. These unreacted materials can provide the source of the hapten. Phthalic anydide (PA), phthalic acid derivatives, and diphenylmethane dusocynate (MDI) will covalently bind to proteins (i.e., in the blood) and can act as an antigen causing immunologic disease under appropriate circumstances. PA may cause asthma, and MDI may cause asthma or hypersensitivity pneumonitis. PA, MDI, or chemicals similar in their capability to react with autologous proteins of the patient could result in an immune response (Patterson et al. 1980). The large number of variables that have an impact on the dialyzed patient makes analysis of the various factors and their relevance to clinical disease complex.

Plasticizers used in the manufacture of dialysis tubing, blood clot traps, and in all devices involving the external circulating of blood may be toxic to patients. The plasticizers and stabilizers employed are: phthalic acid esters, organic tin compounds, epoxidized soya bean oil, dibasic C_1 to C_6 acids, and sobacta compound. It was found that certain patients exhibit a clinical illness simulating "viral hepatitis" shortly after beginning dialysis with new PVC tubing. The hepatitis disappeared when the tubing was changed (Kjellstrand 1978).

In response to the controversy over the leaching of di-2-ethylhexylphthalate, both Dow Chemical Medical Division and Renal Systems Corporation have manufactured tubing for dialysis that does not contain DEHP as its plasticizer. This alternative tubing has been commercially available for at least five years.

Another risk to dialysis patient related to plastic is the introduction into the body of plastic fragments from the tubes. Kletschka _et al_. wrote that "spalled plastic particles are undoubtedly responsible for much of the heart (i.e., subendocardial necrosis 'Stone Heart Syndrome'), brain, and other organ damage...." (Kjellstrand 1978).

Dialysate Composition

The composition of the dialysate used in hemodialysis depends on clinical requirements. However, the components are usually water, electrolytes, glucose, and added nutrients and medications. The accuracy of the dilution is checked by measuring the conductivity, osmolality, or the chloride content.

Water is the largest component utilized in the dialysate. There are extreme geographic variations in potable water supplies regarding hardness, arsenic, and iron content. There are also various methods used to "purify" water: distillation, softness, de-ionization, and reverse osmosis. Extremely pure water requires complicated equipment with more chances of breakdown and contamination. Also, the availability of the proper equipment is somewhat dependent upon the facilities' and/or patients' economic competency. Some of the compounds commonly found in water include: chlorine, copper, nitrate, chlorazine, fluoride, and aluminum (from alum treatment). The latter has been implicated in the onset of a devastating complication called dialysis dementia (Kjellstrand 1978). The advent of alum treatment of water with its resulting increase in aluminum content has been implicated in cluster outbreaks of dialysis dementia in Athens, Newcastle Upon Tyne, Chicago, and some other cities with a high aluminum content in the water supply.

Some new diseases have been identified which may have genetic predispositions aggravated by environmental exposure. An example would be iron myopathy. which is seen in patients with iron overload from too prolonged treatment of anemia, excessive hemolysis, multiple transfusions, or high levels of iron in the water and food supply. The disease is associated with high blood ferritin levels and deposition of iron in the proximal muscles of the legs. HLA-typing suggests some increased risk associated with the same groups that have been implicated in the disease, hemochromatosis.

Chlorine compounds are found in dialysis water and are known to cause moderate to severe hemolytic processes. Chlorine occurs in two principle forms, chlorine and chloramine. Chloramine is the best known toxic element, but both are strongly suspected of causing pathological effects on the reticuloendothelial system. One significant outcome of an impaired reticuloendothelial system is the eventual requirement for blood transfusions (Kjellstrand 1978).

Patients on maintenance hemodialysis are almost invariably anemic. Three mechanisms of red-cell injury are identified as complications of hemodialysis. Oxidant red cell destruction has been found after exposure to dialysate containing such agents as copper, chlorazine, or nitrate. Thermal red-cell injury has been observed, when overheated dialysate was used, with resultant spherocyte formation, increased osmotic fragility, and red-cell destruction (Kjellstrand 1978). Drug-induced hemolysis on a hypersensitivity basis has also been seen.

Medications Used by Hemodialysis Patients and Other Factors

Patients on maintenance hemodialysis are exposed to a multitude of substances which may be toxic, or invoke hypersensitivity. Oral drugs, intravenous medications containing stabilizers and preservatives, blood products, chelating agents in transfused blood, traces of chemicals, such as formaldehyde and ethylene oxide plasticizers from tubing or bags of intravenous fluids, particles of plastics, particles of glass from drug vials, and even particles of rubber from stoppers of multiple dose vials are just a few potential hazards (Hoy et al. 1979).

Ethylene oxide from EO-sterilized equipment can cause systemic allergic reactions, thiouram leached from rubber has caused allergic contact sensitivity in a group of maintenance dialysis patients, and heparin can cause eosinophilia. Anaphlactoid reactions due to nonimmune complex serum protein aggregation have been identified, and a model for this may exist in maintenance dialyzed patients exposed to reinfusion of plasma proteins altered after adherence to and aggregation on the dialyzer membrane. The presence of circulating free DNA during dialysis, and the increased prevalence of antinuclear antibody in maintenance dialyzed patients attest to reinfusion of and sensitization to nuclear material as a result of white cell disruption on the membrane. Formaldehyde reacts with and alters amino acids, proteins, nucleic acids, nucleosides, nucleotides, nucleoproteins, and red cell membranes, rendering them more antigenic (Patterson et al. 1980).

Patients have been reported to experience a clinical manifestation labeled as "new-dialyzer syndrome" which may often go unrecorded. This occurs: 1) because of the complexity of factors that may cause reactions during hemodialysis, including the blood tubing, the dialyzer, the water or concentrate used to make the dialysate, or the intravenous solution used to fill the extracorporeal blood circuit; and 2) because of the variety of agents that could potentially cause adverse reactions, including particulates, plasticizers, stimulant residuals or reaction products, pyrogens, or bacteria. Most dialysis facilities are not equipped to pursue the exhaustive evaluation necessary to define a causative agent in the occasional acute reaction (Ogden 1980).

It is not known whether the body burden of aluminum increases in patients with normal renal function who are given aluminum-containing antacids over an extended time, such as patients with chronic peptic-ulcer disease. However, tissue burdens of aluminum were found to be markedly altered in uremic patients on dialysis receiving aluminum-containing, phosphate-binding gels.

Brain gray-matter aluminum was higher in all patients with the dialysis-associated encephalopathy syndrome than any of the control subjects or the uremic patients on dialysis who died of other causes. With the exception of aluminum, other trace-element abnormalities have not been consistently observed in patients who died of the dialysis encephalopathy syndrome. There is some indirect evidence that this neurologic syndrome may be related to aluminum toxicity (Alfrey 1976).

As part of the hemodialysis process, the patient's blood is heparinized to prevent clotting in the extracorporeal circuit. Heparin causes a reduction of the clotting mechanism, particularly in hemodialysis, and is contraindicated in patients who require surgical procedures and have a faulty clotting mechanism.

These and other agents could all cause sensitization, especially in patients with an atopic diathesis. These profound pathological systemic "shock waves" on the human organism are only a small part of the overall clinical manifestations displayed by the ESRD patient, who usually has a primary clinical syndrome with farreaching compounding "shock waves" of its own. This overall complex situation makes identification of any single cause-effect relationship very cumbersome and scientifically questionable.*

2.2.2 Peritoneal Dialysis

Acute peritoneal dialysis requires an invasive surgical procedure. The procedure is accomplished by inserting a temporary sterile plastic catheter into one of the pelvic gutters and irrigating the peritoneum with sterile solutions. A small stab wound is made in the midline, one-third of the way from the umbilicus to the symphysis pubis. Upon proper placement of the catheter, one liter of solution is infused rapidly and allowed to drain immediately to test the adequacy of drainage. A purse-string suture is placed in the skin around the puncture-site to minimize leakage, a sterile dressing is applied, and the catheter is taped in place and connected to a sterile closed infusion-drainage system.

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*Blackburn and Osweroff interview, 1981, p. 17.

The irrigation schedule is usually organized into inflow, dwell, and outflow periods. Inflow of two liters of solution is usually accomplished within five to ten minutes. The fluid is allowed to remain in the abdomen for a 30-minute dwell period, and is then drained by gravity into a sterile closed system over a period of 15 to 20 minutes. Thus, a single two-liter exchange requires about one hour. Shortening the dwell-time enhances the removal of small molecules, such as urea, but increases the amount of dialysis solution needed. Duration of treatment varies from 24 to 72 hours, depending on clinical indications. Due to the duration of treatment time and because this process is a surgical procedure, peritoneal dialysis is usually accomplished in a hospital setting. Peritoneal dialysis removes fluid efficiently, will not precipitate bleeding, and avoids sacrificing vessels that may later be needed for maintenance dialysis (Guyton 1956).

The placement of a permanent peritoneal catheter (Tenchoff catheter) for chronic peritoneal dialysis also involves a surgical procedure. Placement of a permanent catheter is done by making an incision in the midline and putting the catheter into the peritoneal cavity. These permanent catheters have a felt cuff which is placed above the peritoneal membrane. The felt cuff is sealed by growth of fibrous tissue around it, thus closing the hole to the peritoneal cavity. The catheter is directed out subcutaneously along the abdominal wall two to three inches from the point at which it is inserted into the peritoneal cavity. It then exits from the peritoneal wall skin site.

Chronic peritoneal dialysis involves two-liter exchanges generally speaking every half hour. It requires 40 to 60 hours of the two-liter, half-hour exchanges weekly depending upon the patient's residual renal function. Peritoneal dialysis can easily be performed at home. It is felt that the technique is much less complex than hemodialysis.

The main problem with chronic peritoneal dialysis is infection in the peritoneal cavity (peritonitis). This infection is usually due to poor technique in handling the peritoneal catheter. With use of the chronic indwelling peritoneal catheter (Tenchoff catheter), the occurrence of peritoneal infection has decreased to one to two infections per six to twelve months.

Peritoneal dialysis equipment includes:

- Peritoneal catheter as the entrance/exit mechanism into the peritoneal cavity
- Tubing system used to conduct the ingress and egress of the dialysate solution
- Dialysate component that primarily consists of water, electrolytes, glucose, and added medication as required.

Each of these components, along with an occasionally utilized rotary pump, provide potentialities to the patient similiar to those present in hemodialysis for the introduction of contaminants and adverse iatrogenic reactions.

There are several peritoneal dialysis machines. One is the reverse osmosis peritoneal dialysis machine, which uses a concentrate of peritoneal dialysate similar to that used in hemodialysis. The machine dilutes the concentrate similarly to the hemodialysis machine, and produces a dialysate of composition similar to plasma. Pure water is produced by a reverse osmosis component in this peritoneal dialysis machine. Another type of peritoneal dialysis machine is called the peritoneal cycler, which is a simple machine containing a heating element to heat the peritoneal dialysate fluid and does not use concentrate. This machine uses two-liter bags of peritoneal dialysate and generally can hold eight bags to run four half-hour cycles.

Factors Involved in Selection of Peritoneal Dialysis

Problems concerning the selection of patients for peritoneal dialysis include the establishment of a blood access, the poor or unstable cardiovascular condition of the patient, and psycho-social factors. Peritoneal dialysis is less traumatic to the patient's cardiovascular system than hemodialysis, because there is no reduction in circulating volume or strain on the cardiac output. However, overfilling of the abdomen with elevation of the diaphram can reduce ventilation and increase the symptoms of congestive heart failure. These and other selection criteria, listed in table 2-1, cause many clinicians to prefer peritoneal dialysis to other modalities.*

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*Blackburn and Osweroff interview, 1981, p. 17.

Peritoneal Catheter and Equipment

A significant complication of peritoneal dialysis has been both septic and aseptic peritonitis. Septic peritonitis results when nonhomogenic bacteria are introduced into the peritoneum, while aseptic peritonitis is attributed to the use of equipment sterilants.

In many instances, sterilization of machines utilized for peritoneal dialysis is carried out with formaldehyde and acetic acid. The Gandhi *et al.* (1979) study review found 15 to 30 percent of peritonitis occurring in patients on peritoneal dialysis to be characterized as aseptic in nature. The cause of the peritonitis was ascribed to occasional failure of the reverse-osmosis membrane adequately to remove endotoxin from the input water. Gandhi *et al.* (1979) also found evidence to incriminate the dialysis concentrate as a source of endotoxin. Their most significant find was that both formaldehyde and phenols pass through reverse-osmosis membranes. In addition, they pointed out that these compounds are irritants, and could conceivably cause a sterile peritonitis.

Peritoneal dialysis patients, like their hemodialysis counterparts, must be provided a dialysate with controlled bacterial levels. While peritoneal dialysis patients also must be provided a sterile pyrogen-free dialyzing fluid, the complexity of the extracorporal circuits and the frequency of the patients' exposure to them affords great opportunity for the common, but complex, problems of sepsis and pyrogen reactions in the dialysis population.

Tubing System Component

The tubing utilized for peritoneal dialysis is similar to that of the tubing used in hemodialysis. However, it is agreed that there is little contact between blood and peritoneal dialysate or peritoneal dialysis tubing, except for the indwelling Tenchoff permanent peritoneal catheter. This catheter may contact structures in the peritoneal cavity, including the omentum and the intestines, as well as the site of catheter placement. It is possible under certain circumstances that blood may contact the Tenchoff catheter, if the layer of peritoneum covering the omentum and the intestines is exposed.

The peritoneal dialysis patient is exposed to approximately 3 to 5 mg. of DEHP per treatment day (Harris 1981).

Dialysate Component

The composition of a typical commercially available peritoneal dialysis solution mimics the electrolyte composition of interstitial fluid, but differs in that acetate replaces bicarbonate. Heparin, sodium and, if needed, potassium chloride also may be added to peritoneal dialysate.

Glucose, which is absorbed from the peritoneum, can be used as an osmotic force to balance the oncotic pressure in the plasma and to produce ultrafiltration in higher concentrations. All peritoneal dialysis solutions are prewarmed to 37 degrees Celsius to promote efficient diffusion and prevent cooling of the patient with resulting vasoconstriction. The latter may induce abdominal pain, abdominal cramps, and also impair the efficiency of the diffusion exchange.

The same dialysate problems faced by the hemodialysis patient are generally true for the peritoneal dialysis patient, although in peritoneal dialysis the dialysate enters the peritoneal cavity, providing a much slower absorption ratio for contaminants than the blood route used by the hemodialysis patient.

Medications Used by Peritoneal Dialysis Patients and Other Factors

Like hemodialysis patients, peritoneal dialysis patients also face an onslaught of medications and other additives during their dialysis. Medications may be added directly to the two-liter bags of peritoneal dialysate fluids, especially for those patients on a cycler or who are receiving acute peritoneal dialysis with a manual technique.

Patients who are on a reverse osmosis peritoneal machine use concentrate, and thus do not often have additives added to their solution. However, the effect of the burdens on their systems is of no less consequence than that discussed earlier in the hemodialysis section (table 2-2).

2.2.3 Continuous Ambulatory Peritoneal Dialysis

Continuous ambulatory peritoneal dialysis (CAPD) utilizes the continuous presence of dialysate fluid in the peritoneum, 24 hours per day, seven days per week. Dialysate is drained from the abdomen and replaced with fresh solution three to five times each day. The schedule of solution exchange is adjusted to meet individual patient needs. However, daytime exchanges usually last from four to six hours and the overnight exchange from 8 to 12 hours.

CAPD is a closed system consisting of the peritoneal cavity, a chronic indwelling Tenchoff catheter, a 42-inch-long connecting tugin, and the collapsible dialysate bag (Fraedrick et al. 1980). The empty dialysis solution bag and tubing are folded compactly and carried in the clothing or in a small fabric pouch until time for drainage of the dialysate solution. Drainage is accomplished by gravity, and the filled bag is disconnected and discarded. Then, another bag is attached from an elevated position for the inflow cycle. No machinery is required.

CAPD has been found to be a better dialysis modality for treatment of acute renal failure for patients who have severe cardiovascular disease and for those who have had cardiovascular intervention. This is because hemodialysis often results in a negative influence on the often critical hemodynamic situation of the patient.

Intermittant dialysis, especially hemodialysis, seems to be disadvantageous because of its relatively short and intensive elevation of perenal substances. By comparison, CAPD guarantees a continuous exchange of metabolites and volume, comparable to physiological renal performance.

A variation of CAPD called CCPD, or continuous cyclic peritoneal dialysis, is employed when daytime exchanges are inconvenient or impossible for the CAPD patient because of working conditions. Suitable clearances of nitrogenous wastes of metabolites are obtained by using a single all-day peritoneal exchange, and then connecting the catheter to a continuous cycling machine during the sleeping hours in order to increase the efficiency of the nocturnal period.

Factors involved in Selection for CAPD

CAPD requires strict aseptic conditions in exchanging the dialysis solution and connecting tubing. If this is violated, peritonitis is sure to follow (Fraedrick *et al*. 1980).

CAPD is a relatively new technique with a highly selective criteria and, therefore, limited general use. Current estimates suggest its suitability for from 20 to 35 percent of the ESRD population. The patient goes through an extensive evaluation process and, if selected as a CAPD patient, undergoes a teaching program which addresses the understanding of peritoneal dialysis, dialysate solutions, cycle times, dietary requirements, medications, fluid balance, techniques of monitoring weight and vital signs, procedures, complications, catheter care, and procedures for ordering supplies (Fraedrick *et al*. 1980).

CAPD patients tend to have higher hematocrits, improved energy, and have a more desirable lifestyle because of the freedom from the machine, the ability to travel, take holidays, vacations, etc. Because of its relative simplicity, flexibility, and recent significant increases in the availability of supplies, technology, and third-party payment, CAPD will probably become the dialysis modality of choice for patients who meet the criteria. Table 2-1 lists these and other selection criteria per modality.

The processes, materials, and toxic substances to which the CAPD patients are exposed are the same as those in patients receiving peritoneal dialysis (table 2-2). Many of these also are common to the hemodialysis patient. The basic exception would be the length of exposure and the individual patient's level of involvement in their own treatment modality. However, peritoneal dialysis and CAPD patients were initially found to exhibit a high incidence of peritonitis.

Lately, there has been an appreciable decline in the incidence of peritonitis, which is due possibly to a stricter adherence to the criteria for sterile conditions required during the preparation and changing of the dialysis bags by CAPD patients. There has also been improvement in the adapter technology with the introduction of the teflon connectors. Large current programs are reporting total incidence of cloudy return fluid in the range of one episode per 6-8 patient months of CAPD experience. There are currently over 2,500 patients on CAPD in the United States, 120 in the group monitored by the New York State Institute and 70 in a single program in the Washington D.C. area.

CHAPTER 3

TOXICOLOGICAL FACTORS OF DEHP EXPOSURE IN RENAL DIALYSIS PATIENTS

P. Wagner, M.S., and I. Marks, M.P.H.

Because DEHP produces toxic effects similar to those produced by a host of other chemicals and medical conditions, it is unlikely that DEHP can be identified as either a primary or secondary cause of toxic symptoms in dialysis patients. While the human effects of ingesting DEHP have been reported to be minimal, animal studies have shown DEHP to produce mild liver dysfunction. Preliminary results of a two-year bioassay suggest DEHP may be a hepatocarcinogen. However, dialysis patients are generally in poor health and subject to a multiplicity of drug therapies. The symptoms of disease plus the toxic effects of any one or a combination of drugs may confound, mask, or act synergistically with DEHP to produce similar toxic effects.

This chapter addresses the toxicity of di-2-ethylhexylphthalate (DEHP) in humans and the feasibility of an epidemiologic investigation of mortality and morbidity caused by such exposure in a population of renal dialysis patients. DEHP is a plasticizer commonly used in blood storage bags, medical tubing, and other medical paraphernalia used in dialysis treatment. DEHP is a phthalate ester prepared from the reaction of phthalic acid with the alcohol, 2-ethyl hexanol. Phthalate esters are primarily used as plasticizing agents in polyvinyl chloride (PVC) to give the polymer its flexibility and softness, and may account for up to 40 percent of the final weight of the PVC product. DEHP and its isomer, dioctyl phthalate (DOP), are currently the most widely used plasticizers (Autian 1973). The chapter discusses the following topics:

- Animal toxicity of DEHP
- Biodistribution of DEHP
- Relevant animal studies
- Extrapolation to human health effects
- Synergistic effects of DEHP with contaminants or drugs
- Confounding effects of medical problems in end stage renal disease.

The likelihood of identifying DEHP effects in an epidemiologic study of dialysis patients is then assessed.

Although DEHP is insoluble in water, it is soluble in organic solvents and oils. Because DEHP is not chemically bound, but only dispersed in the polymer matrix, it can be leached out by solubilizing substances. Human blood plasma is such a substance. The solubility of DEHP in human blood plasma has been reported to approach 5 mg/ml (Miripol et al. 1976). Dialysis patients are known to receive relatively high exposures to DEHP leached from the plastic tubing used in dialysis treatment.

3.1 REVIEW OF DEHP TOXICITY IN ANIMALS

Acute toxicity data for DEHP indicates that the compound is relatively nontoxic when exposure results from a one-time dose. The values for the LD50 range from 2 to 31 g/kg for intraperitoneal injections in rats to 128 g/kg for intraperitoneal injections in mice. The oral LD50 for rats and rabbits is reported to be 30 g/kg (Rubin et al. 1973). Humans have reportedly ingested up to 10 g DEHP and experienced either mild diarrhea or no effects (Shaffer et al. 1945).

Longer term studies on experimental animals have shown some decrease in growth patterns and alteration in liver and kidney weights, when the animals were fed doses of DEHP from 200 to 3400 mg/kg (Shaffer et al. 1945, Carpenter et al. 1953, Nikonorow et al. 1973).

Sherman rats were fed 0.02, 0.06, and 0.20 gm/kg DEHP in their diets for 13 weeks. Growth retardation was reported and ratios of liver and kidney weight to body weight were increased, but no significant histopathologic or hematologic changes were noted (Shaffer et al. 1945).

In a three-month study on rats, a dose of 3.4 g/kg/day showed only weight loss and diarrhea. A 12-month study, using the same dosage, produced a decreased weight gain and liver enlargement (Nikonorow et al. 1973). In a 14-week study on dogs, one animal gavaged with 5 gm/kg/day DEHP showed some chronic cholecystitis. However, this animal as well as the others in the experiment had normal hematology and organ weights (Harris et al. 1956). In a study where rats were dosed IV with 250 to 300 mg/kg DEHP dissolved in surfactants, the animals showed acute respiratory distress and hemorrhagic congestion (Schultz et al. 1975).

More recent studies have focused on the biochemical measurement of the toxic effects of DEHP exposure. These studies have shown lowered serum cholesterol levels and inhibitory effects on hepatic lipid biosynthesis. Male Sprague-Dawley rats were fed diets containing one and two percent DEHP for 21 days (Bell et al. 1978). The animals were then killed and the tissues analyzed. The liver weights, expressed as a percentage of body weights, were increased 70 percent above control values. Serum cholesterol levels were significantly lowered (78 percent of control value) by the seventh day of exposure to DEHP and this low value was maintained throughout the 21-day study. Liver cholesterol values in the rats fed DEHP did not differ significantly from the values for the controls.

The investigators noted an inhibitory effect on hepatic lipid biosynthesis as determined by decreased incorporation of ^{14}C-acetate into hepatic lipids. An inhibition of phospholipid and triglyceride biosynthesis was postulated to be related to an impairment of fatty acid esterification. Livers from rats fed 0.5 percent DEHP for nine days showed reduced uptake of ^{3}H-oleate. These effects confirmed earlier results by Bell and Nazir (1976).

In the earlier study, the investigators examined the effect of 0.5 percent dietary DEHP on the incorporation of ^{14}C-acetate in lipids by rat kidneys. They reported a significant decrease of incorporation of ^{14}C-acetate only in the triglyceride and sterol ester + hydrocarbon fraction. In another experiment (Bell et al. 1976), the kidneys of rats fed one percent DEHP in their diet for 18 days did not differ significantly in their ability to incorporate ^{14}C-acetate into total lipids. The authors interpreted the experimental results as an ability of the kidney to normalize alterations in lipid metabolism.

Preliminary and unreviewed reports from the National Cancer Institute, Information Division, suggest that DEHP may be carcinogenic. A two-year chronic feeding study of DEHP produced hepatocellular carcinomas and neoplastic nodules in male and female rats, and adenomas and hepatocellular carcinomas in male and female mice. However, the doses used in this study were high--6,000 and 12,000 ppm for rats and 3,000 and 6,000 ppm for mice. Extrapolation of the effects seen at those dose-levels to patients receiving doses orders of magnitude lower is tenuous.

3.2 BIODISTRIBUTION

Biodistribution studies in vivo have been reported where radioactive DEHP was administered either orally or by IV. Because DEHP is insoluble in water, many of these studies used a variety of solubilizing or emulsifying agents. These agents appear to have affected the distribution of DEHP in the tissue.

Stein et al. (1974) reported DEHP accumulated in significant amounts in the heart and epididymal fat pads when fed to rats at 0.1 percent in the diet. Schultz and Rubin (1975) reported that 200 mg/kg DEHP emulsified in albumin was found in high concentrations in the liver, moderate concentrations in the lung and spleen, and low concentrations in the fat and kidney. However, mice dosed at 115 mg/kg IV with DEHP in serum had high concentrations of the chemicals in the liver and kidney and low concentrations in the lung, spleen, and fat (Thomas et al. 1978, Waddell). Rats dosed at 600 mg/kg IV with DEHP solubilized with oleic acid were reported to have high concentrations of the chemical in the liver and lung, but low concentrations in the spleen and fat.

In addition to the effect of the solubilizing and emulsifying agents on distribution patterns, they also appear to produce toxic effects themselves and with DEHP. Rubin (1975) studied the effects of intravenous doses of DEHP solubilized in a 13 percent aqueous solution of detergent on the blood pressure in rats. In some cases, doses at 80 to 100 mg/kg resulted in blood pressure falling below 30mm Hg, causing death. Doses of 40 mg/kg resulted in a drop in blood pressure of 18 to 27 mm Hg. However, detergent alone will cause a hypertensive reaction when injected IV and DEHP produces a hypotensive effect administered by the same route. Thus, the drop in blood pressure, when the solubilized DEHP is administered, is the resultant of the two contrary effects. The ability of DEHP to induce hypotension is greater than the hypertensive effect of the detergent.

DEHP is thought to metabolize to water-soluble acids, alcohol, and ketones that are excreted in the urine of normal animals and humans (Albro et al. 1973, Daniel et al. 1974). The clearance is about 60 to 90 percent in 24 hours (Rubin et al. 1976).

DEHP has been found in the adipose tissue, liver, brain, heart, lung and spleen of experimental animals and humans (Rubin, et al. 1973, Thomas et al. 1978, Waddell, Stein et al. 1974). No data has been found on the retention and storage of the metabolites by either nephrectomized experimental animals or dialysis patients. However, in one study (Chen et al. 1978), nephrectomized dogs were injected IV with 225 mg/kg DEHP. Analyses of serum showed that levels of DEHP in the nephrectomized dogs were higher for a longer period of time than in control dogs. The 72-hr and 96-hr serum concentrations of DEHP were similar in both groups. The investigators interpreted this finding as likely evidence of storage and/or metabolism of DEHP by nephrectomized dogs, but postulated no metabolic pathway. The dogs were killed after four days and their tissues analyzed for DEHP. The highest tissue concentration was found in the lungs in both nephrectomized and control dogs.

Human kidneys from 17 persons dying of causes other than renal failure were analyzed for DEHP (Overturf et al. 1979). Extent and duration of exposure to DEHP was unknown in each case. Two kidneys were diagnosed as nephrosclerotic; the remaining 15 were normal. Both nephrosclerotic kidneys contained measurable amounts of DEHP in the cortical and medullary tissues, but DEHP was found in only two of the normal kidneys. The authors presented no explanations for their findings. Any conclusions based on these findings are difficult, since extent or duration of exposure to DEHP is unknown. The chronic toxicity of the metabolites is not known, since in normal circumstances they are rapidly excreted.

Stern et al. (1977) demonstrated that the disposition and effects of DEHP can be dependent upon dosage and the form of administration. In a series of experiments, DEHP was emulsified with a surfactant, or solubilized in ethanol and added to plasma, or leached by plasma from polyvinyl chloride plastic. Groups of rats (15 each) were then injected with 2.5 mg/kg of DEHP in each form, including the DEHP-surfactant form undiluted with plasma. Kinetic studies performed with ^{14}C-DEHP showed that the leached DEHP had the most rapid clearance.

The kinetics followed a biphasic pattern, with the half-lives for the second phase showing the leached form as having a significantly reduced half-life over the other administered forms (31 minutes vs. 263, 83, and 181). An examination of tissue residues showed a greater retention by the liver, lungs, and spleen of the non-leached forms of DEHP than the leached form. The investigators postulated that the excretion rates of DEHP would probably be different since organ retention of the compound differed. Analyses of urine and feces showed that in the first seven hours after infusion the leached DEHP was excreted at approximately twice the rate of the emulsified compound, but from 14 to 44 hours the rates were approximately the same.

The investigators conclude that experiments designed to elucidate the effects of DEHP in humans should parallel actual human doses and dosage forms as closely as possible. Using doses or dosage forms not encountered by man may well introduce artifacts into the evaluation which will inhibit or distort a valid conclusion.

In summary, animal studies, primarily feeding studies, using doses of DEHP of 20 to 5,000 mg/kg daily produced the following effects: reduced weight gain, increased liver and kidney weights, lowered serum cholesterol, inhibition of hepatic lipid biosynthesis, and a transitory decrease in the renal lipid biosynthetic process. However, as shown by Stern et al. (1977), routes of exposure and doses not consistent with actual exposure oftentimes lead to erroneous interpretations, as well as altering experimental results. For these reasons, the only studies considered to be relevant to dialysis patients are those where the DEHP dose is actually leached from PVC tubing or plastic bags. These relevant studies are discussed below.

3.3 RELEVANT ANIMAL STUDIES

Miripol et al. (1976) injected rats with plasma containing 1.0 and 3.7 mg DEHP/kg twice a week for 63 days. The authors state that a dose of 3.7 mg/kg is equivalent to what a 70 kg human would receive in an exchange transfusion of 21-day-old blood. Rats injected with serum or not injected at all were used as controls. Rats from each group were killed after eight injections and 19 injections, or 63 days after the last injection. No significant differences were seen for the following parameters in rats treated with DEHP: survival rate, growth rate, general behavior, hemograms, serum chemistry values, liver functions, absolute or relative organ weights, plasma and tissue levels of DEHP, or gross and microscopic pathology.

The effects of DEHP on rhesus monkeys undergoing chronic transfusion therapy were studied by Jacobson et al. (1977). Immature rhesus monkeys were divided into the following groups: three monkeys were transfused weekly with 15 ml of platelet-rich plasma stored in PVC; two monkeys were transfused biweekly for six months with 15 ml of platelet poor plasma stored in PVC; two monkeys were transfused weekly for six months with 15 ml of platelet-rich blood stored in polyethylene; three monkeys were not transfused. The monkeys received dosages of DEHP of 6.6 to 33 mg/kg. This amount compares favorably (2.1 to 27.5 mg/kg) to the amount of DEHP received by human pediatric patients monitored for one year.

Serum chemistries, histopathology, and liver-spleen scans were used as diagnostic tools. Serum chemistries obtained at four-month intervals were normal throughout the course of the experiments. Liver-spleen scans showed decreased activity ratios in three monkeys transfused with PVC-platelet-rich plasma after three months of treatment, which persisted 14 months after termination of the experiment. Plasma disappearance curves for BSP follow a single, exponential function for immature primates and human children.

Adults, both human and primate, exhibit a biexponential function. Children with asymptomatic liver disease, for example cystic fibrosis accompanied by hepatomegaly, will follow a biexponential function. In this present study, BSP transport was used as an indicator of liver abnormality. Three of the five monkeys who received the PVC-platelet-rich blood demonstrated biexponential disappearance curves after one year of transfusion therapy. Fourteen months after cessation of treatment, the three monkeys still had biexponential disappearance curves. Liver biopsies showed abnormal histologic findings in four of the five monkeys transfused with PVC-platelet-rich plasma. Followup biopsies at five and 14 months after cessation of treatment showed diffuse portal lymphotocytic infiltration, hepatic necrosis, and evidence of binucleate cells. The effects seen in PVC-plasma were not seen in the control animals.

In summarizing the effects seen in monkeys, only the BSP clearance and the liver-spleen scan are routinely performed on living human subjects. Abnormal results for these procedures can be caused by a variety of clinical conditions and/or exposure to numerous chemicals. For example, abnormal BSP clearance can occur with infectious hepatitis or portal cirrhosis.

3.4 EXTRAPOLATION TO HUMAN HEALTH EFFECTS

Extrapolation of animal data on health effects to humans should be done with care. Factors to be considered include:

- Do the animals metabolize the chemical in a manner similar to humans?
- Are the biodistribution and bioaccumulation patterns similar?
- Are the toxic signs the same?
- Are dose-response curves similar?
- Are the animal experiments designed so that the exposure route and dosage are valid for human exposures?

Obviously, the answers to the above questions should be "yes" in so far as possible.

However, other more basic problems are also present. Test animals of the same species and strain are generally extremely similar genetically, especially rats and mice. These two species, used widely to test chemicals, have little innate resistance to diseases, develop many varieties of spontaneous tumors, and may be chronically infected with respiratory diseases or hepatitis. Extrapolation of data derived from these genetically-similar animals to humans, who are genetically dissimilar, should be done carefully.

In addition, test animals are kept in controlled environments, and fed controlled diets. Humans, on the other hand, are exposed to a variety of environments and differ widely in their dietary habits. Humans also expose themselves to drugs and pollutants which may or may not act synergistically. Finally, humans appear to have detoxification mechanisms that are more sophisticated than those of most animal species. A toxic effect seen in animals may not necessarily be present in all humans similarly exposed.

3.5 TOXICOLOGICAL ENVIRONMENT OF DIALYSIS PATIENTS

Dialysis patients are often in poor health. They may have a variety of other clinical conditions, including hepatitis, diabetes, cancer, cardiovascular disease, arthritis, etc. A survey conducted of hospitalized chronic hemodialysis patients in 27 dialysis centers in Michigan (Mayor et al. 1979) showed that 11.4 percent of the patients carried the Hepatitis B surface antigens distributed in 21 of the 27 dialysis units. Antibodies for the Hepatitis B antigen was found in 31 percent of the patients from selected units. The survey also showed that 26 percent of the Hepatitis B antigen carriers had not been previously identified. Some of this information is addressed in detail in Task Report No. 1.

Dialysis patients are also routinely exposed to multiple drug therapies. Heparin, an anticoagulant, is routinely given to dialysis patients. Gelfand et al. (1978) have reported that free thyroxine levels rise after heparin administration for hemodialysis. Heparin is also thought to antagonize the action of ACTH, insulin, and corticoids. Dialysis patients that are candidates for renal transplants may be treated with immunosuppressant drugs such as azathioprine, which may cause liver damage characterized by elevated alkaline phosphatase levels and slightly elevated bilirubin. Patients treated with immunosuppressants may ultimately develop cancer and be treated with chemotherapeutics such as methotrexate, which is a hepatotoxin and may cause liver atrophy, necrosis, cirrhosis, and periportal fibrosis. In addition, dialysis patients may be routinely administered drugs such as tranquilizers, barbiturates, and analgesics which may or may not be synergistic with DEHP and routine drug therapies.

DEHP is reported to show synergistic effects with pentobarbital and methaqualone (Seth et al. 1977). Since these compounds are CNS depressants, synergism may exist with other CNS depressants as well.

In addition to the various clinical conditions that affect dialysis patients and the toxic effects caused by routine drug therapies, the dialysis patient is exposed to other toxic chemicals present in the dialysis equipment and assorted support chemicals. The PVC tubing used in hemodialysis units has calcium, zinc, and tin added as stabilizers (Geertz et al. 1974). The concentrations of these stabilizers range from 110 to 31 ppm for zinc to approximately 0.3 ppm for tin and 102 to 2.5 ppm for calcium.

These metals may be leached from the medical devices during the dialysis procedures. Ionized calcium leached into blood or serum may cause such problems as soft tissue calcification and depression of phosphorus levels in the blood. Cadmium, because of its chemical similarity to zinc, generally occurs as a trace impurity in zinc and zinc products. Cadmium is a nephrotoxin and is stored in the body in the kidneys. Its effects are cumulative. The dialysis machine itself may release copper, which is reported to cause hemolysis and fever (Kjellstrand 1978). Sterilizing agents used on membranes and filters commonly contain formaldehyde (Kjellstrand 1978, Orringer et al. 1976, Sandler et al. 1979, Fassbinder et al. 1979). The exposure of dialysis patients to the formaldehyde in these solutions has been implicated in hemolysis due to the induction of anti-N or anti-N-like antibodies (Sandler et al. 1979, Fassbinder et al. 1979).

The water used in dialysis may also contain numerous impurities (Kjellstrand 1978). Because of the extreme geographic variations, the trace impurities in water naturally vary greatly from location to location.

Contaminants can also vary because of industrial activity which may discharge chemicals into water used as municipal water supplies. The efficiencies of individual water treatment plants is also a consideration in the levels and types of trace contaminants in water used in dialysis treatment. Most water treatment facilities add chlorine or chloramine to the untreated water. Chloramine may cause methemoglobin formation with further oxidation to Heinz Bodies. Heinz Bodies may accumulate and predispose erythrocytes to destruction by the spleen (Kjellstrand 1978). Chlorine may be contaminated with carbon tetrachloride, a hepatotoxin and suspect human hepatocarcinogen. Organic chemicals present in untreated water may undergo chlorination to form chlorinated compounds such as chloroform, a hepatotoxin and suspect human carcinogen.

Trace metals found in drinking water include aluminum, arsenic, iron, cadmium, zinc, and copper. The actions and interactions of these metals with each other or the other chemicals dialysis patients are exposed to are not known. Aluminum, however, is suspected of causing dialysis dementia (Kjellstrand 1978). The reasons are four-fold:

- Body storage of aluminum is higher in dialyzed uremic patients as compared to dialyzed patients for other causes
- Compartmentalization of aluminum differs in dialyzed uremic patients from that of other dialyzed patients
- The occurence of the syndrome can be related to naturally occuring aluminum-contaminated water
- The syndrome is preventable by removing aluminum.

3.6 CONCLUSION: FEASIBILITY OF ASSESSING DEHP EXPOSURE AMONG DIALYSIS PATIENTS

In summary, a review of toxicity data for DEHP suggests the compound may produce some generalized liver abnormalities in normal experimental animals. Dialysis patients are exposed to DEHP due to its leaching into their blood from plastic tubing and bags used in dialysis. Although data show the major amount of the compound is metabolized to water-soluble products and excreted fairly rapidly in the urine, no data are available on these processes in either nephrectomized animals or dialysis patients.

Thus, it is possible that the compound and/or its metabolites may be stored in various tissues of the body or be excreted in other ways. Since excretion of the metabolites in urine is not possible in dialysis patients, the pharmacokinetics or metabolic pathways may be altered. Thus, it is conceivable that the toxic effects seen in normal animals and humans may not be representative of the effects produced in this special population.

Further confounding factors are the general poor health of dialysis patients, the multiplicity of drug therapies to which they are exposed, and inadvertent exposures to both chemicals and disease because of the dialysis treatments. Any one of these factors could mask, mimic, or act syngeristically with DEHP to produce toxic effects. Finally, given the general, non-unique toxic effects of DEHP, it is not likely to be possible to identify this chemical as either a primary or synergistic cause of liver abnormalites or other toxic symptoms of dialysis patients.

CHAPTER 4

AN ASSESSMENT OF THE UTILITY OF ESRD MIS DATA FOR EPIDEMIOLOGIC RESEARCH

I. Marks, M.P.H., C. Steele, A.R.T., and
D. Wellington, Ph.D., et al.*

This chapter assesses the utility of the Health Care Financing Administration's (HCFA) End Stage Renal Disease Medical Information System (ESRD MIS) data base for conducting epidemiologic research on persons with chronic renal failure. The discussion is presented in two sections. In the first section, ESRD MIS data are discussed in terms of the elements of the ESRD MIS, the data collection system and its intended uses. The second section addresses the difficulties involved in considering ESRD MIS data as a basis for epidemiologic research. Based on these data, the report concludes that the ESRD MIS lacks the accuracy, consistency, and completeness necessary to perform any meaningful analysis other than demographic analysis.

Since its advent in 1973, the Health Care Financing Administration's End Stage Renal Disease Medical Information System has undergone a number of major changes as to where, when, and how data are collected and stored. As a result of these system changes, the type and quality of the data has been greatly compromised. The purpose of this document is to describe the ESRD MIS data base as it existed in the years 1977 through 1979, and to determine what type of analyses can be performed given the specificity, completeness, consistency, and accuracy of the data files.

4.1 THE END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM: AN OVERVIEW

The End Stage Renal Disease Program was established by Public Law 92-603 in 1972. From 1973 to 1977 the ESRD MIS was administered by the Public Health

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Service. In 1977, the Health Care Financing Administration (HCFA) was assigned responsibility for the Program. Beginning in 1973, patient history data along with billing information were collected under the auspices of the Medicare Program. In 1976, the Medical Information System and its inclusive components were added. The Program is currently administered by the Health Care Financing Administration, Department of Health and Human Services.

The ESRD MIS, a component of the Program, is a nationwide administrative reporting system with a limited amount of general medical information included. The system is used as a management tool to predict trends, distribution, and utilization of services, and to assist in assessing performance under legislative and regulatory mandates. The system also functions as a locating system and may be useful as an index to assist in identifying certain populations. In its present form, the ESRD MIS is of only limited value as a source of accurate statistical incidence data.

Prior to 1973, registries were maintained by the American College of Surgeons (the Renal Transplant Registry) and Research Triangle Institute (the National Dialysis Registry). Historical data from these registeries were transferred to form the basis of the ESRD MIS in 1973. Major modifications in the system were instituted after 1976, and additional revisions are currently underway.

During the period, 1977, 1978, 1979, and January to June 1980, eleven documents comprised the MIS and its complementary systems including the following:

- ESRD Patient History and Treatment Plan
- ESRD Outpatient Dialysis Service Information
- ESRD Transplant Tissue Typing Information
- ESRD Death Notification
- ESRD Center Patient Listing
- Inpatient Hospital and Skilled Nursing Facility Admission and Billing, SSA-1453

- Provider Billing for Medicare and Other Health Services, SSA-1483
- Carrier Payment Records
- ESRD Facility Survey
- ESRD Cost Questionnaires
- ESRD Notices of Approval for Rendering ESRD Services/Demographic and Reimbursement Parameters.

The following subsections of this section address the flow of information to the ESRD MIS, describe the patient population, detail the content and accuracy of the data elements and summarize the problems with the ESRD MIS dataset.

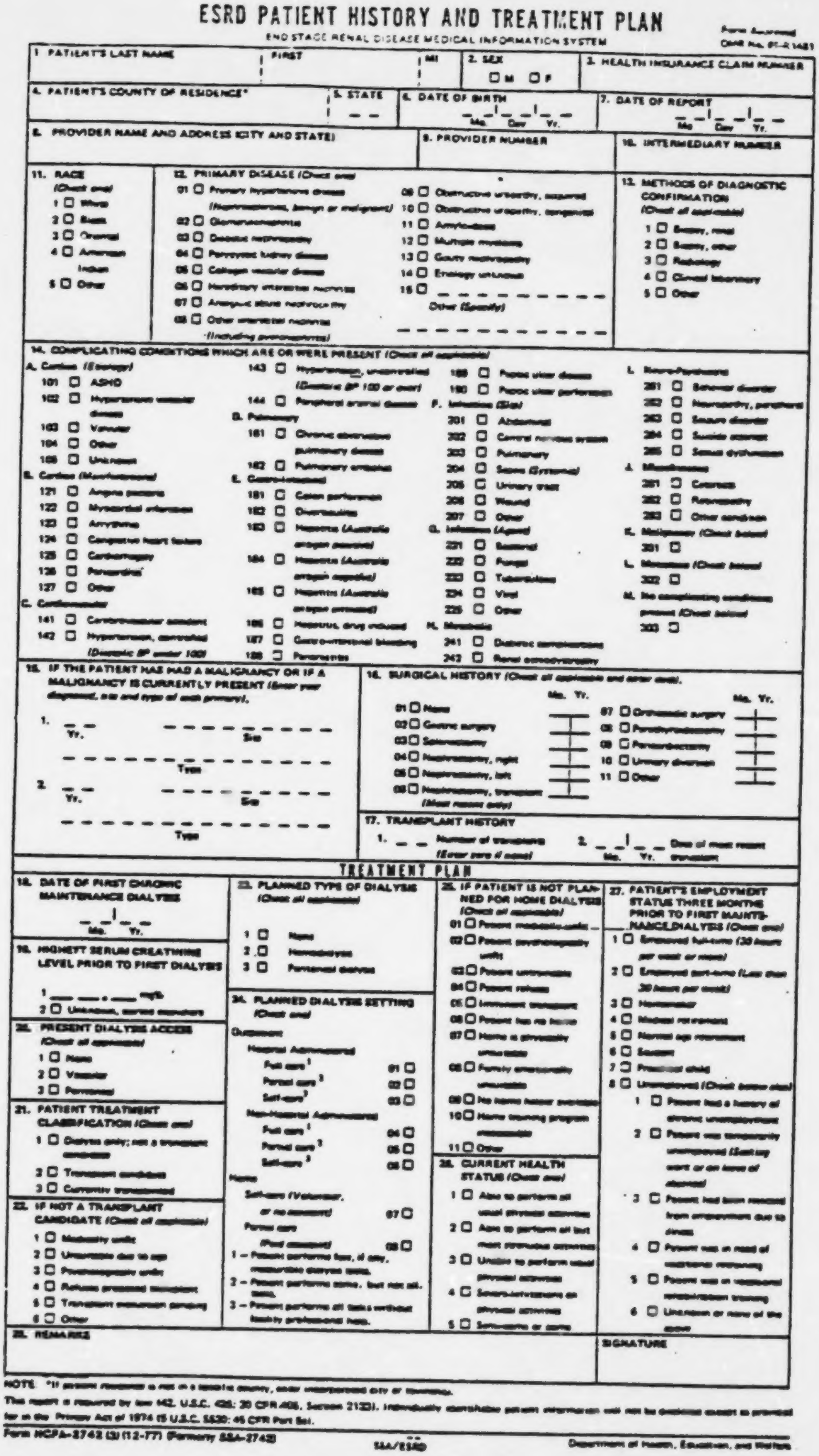
4.1.1 The Flow of Information

The Social Security Administration (SSA) identifies and accretes ESRD patients to their file. When an ESRD patient applies for Medicare benefits, a Form SSA-2728, Chronic Renal Disease Medical Evidence Report, is completed and sent to the SSA. The information on this form is utilized in making an entitlement decision. The form remains in the patient's disability folder at SSA, but its information is not conveyed to ESRD MIS.

At the time of first Medicare inpatient or outpatient billing, an ESRD Patient History and Treatment Plan, HCFA-2742 (figure 4-1), should be completed and sent to the ESRD MIS. For most patients, this occurs once. However, certain circumstances can result in subsequent entries for a single individual. If, for example, a dialysis patient is transplanted, losing Medicare benefits, and later rejects, returning the dialysis, another history must be submitted at the time of the first billing for any new entitlement period.

The ESRD Outpatient Dialysis Service Information form (figure 4-2) is submitted each time a bill is prepared for outpatient services; for most maintenance dialysis patients, this would be once a month.

Figure 4-1. ESRD PATIENT HISTORY AND TREATMENT PLAN



ESRD PATIENT HISTORY AND TREATMENT PLAN

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM

1. PATIENT'S LAST NAME | FIRST | MI
2. SEX ☐ M ☐ F
3. HEALTH INSURANCE CLAIM NUMBER
4. PATIENT'S COUNTY OF RESIDENCE*
5. STATE
6. DATE OF BIRTH Mo. Day Yr.
7. DATE OF REPORT Mo. Day Yr.
8. PROVIDER NAME AND ADDRESS (CITY AND STATE)
9. PROVIDER NUMBER
10. INTERMEDIARY NUMBER
11. RACE
12. PRIMARY DISEASE
13. METHODS OF DIAGNOSTIC CONFIRMATION
14. COMPLICATING CONDITIONS WHICH ARE OR WERE PRESENT

101 ☐ ASHD

15. IF THE PATIENT HAS HAD A MALIGNANCY OR IF A MALIGNANCY IS CURRENTLY PRESENT

1. Yr. Site Type

2. Yr. Site Type

16. SURGICAL HISTORY

17. TRANSPLANT HISTORY

TREATMENT PLAN

18. DATE OF FIRST CHRONIC MAINTENANCE DIALYSIS Mo. Yr.
19. HIGHEST SERUM CREATININE LEVEL PRIOR TO FIRST DIALYSIS
20. PRESENT DIALYSIS ACCESS
21. PATIENT TREATMENT CLASSIFICATION
22. IF NOT A TRANSPLANT CANDIDATE
23. PLANNED TYPE OF DIALYSIS
24. PLANNED DIALYSIS SETTING
25. IF PATIENT IS NOT PLANNED FOR HOME DIALYSIS
26. CURRENT HEALTH STATUS
27. PATIENT'S EMPLOYMENT STATUS THREE MONTHS PRIOR TO FIRST MAINTENANCE DIALYSIS
28. REMARKS

SIGNATURE

NOTE: *

Form HCFA-2742 (3) (12-77) (Formerly SSA-2742)

SSA/ESRD

Department of Health, Education, and Welfare

FIGURE 4-2. ESRD PATIENT DIALYSIS SERVICE INFORMATION

ESRD OUTPATIENT DIALYSIS SERVICE INFORMATION

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM

Form Approved
OMB No. 68-R1431

1. PATIENT'S LAST NAME | FIRST | MI
2. SEX ☐ M ☐ F
3. HEALTH INSURANCE CLAIM NUMBER
4. PATIENT'S COUNTY OF RESIDENCE*
5. STATE — —
6. DATE OF BIRTH __ __ | __ __ | __ __ Mo. Day Yr.
7. STATEMENT COVERAGE PERIOD from __ __ | __ __ | __ __ Mo. Day Yr. thru __ __ | __ __ | __ __ Mo. Day Yr.
8. PROVIDER NAME AND ADDRESS (CITY AND STATE)
9. PROVIDER NUMBER
10. INTERMEDIARY NUMBER

11. ☐ CHECK HERE IF THE ATTACHED BILL INCLUDES NO CHARGES FOR DIALYSIS TREATMENTS OR SUPPLIES, AND SKIP TO ITEM 25.

12. DIALYSIS SETTINGS *(Check the patient's usual setting. If his usual setting changed during the month, check both. If the patient was dialyzed in any setting on a temporary basis, check the appropriate block(s) in the temporary column also).*

☐ Check here if treatment was provided under an all-inclusive rate, and do not complete IV and V below.

	I. Usual (Check)	II. Temp. (Check)	III. Total Dialysis Sessions	IV. Charge Per Dialysis	V. Total Dialysis Charges
OUTPATIENT					
Full care[1]	a ☐	b ☐	c ____	d ____	e ____
Partial care[2]	f ☐	g ☐	h ____	i ____	j ____
Self-care[3]	k ☐	l ☐	m ____	n ____	o ____
Self-care training	p ☐	q ☐	r ____	s ____	t ____
HOME					
Self-care *(Volunteer, or no assistant)*	u ☐	v ☐	w ____		
Partial care *(Paid assistant)*	x ☐	y ☐	z ____		

1 — Patient performs few, if any, measurable dialysis tasks.
2 — Patient performs some, but not all, tasks.
3 — Patient performs all tasks without facility professional care.

ROUTINE LABORATORY TESTS

13. IN-UNIT CHARGES $________

14. OUT-OF-UNIT CHARGES $________

HOME DIALYSIS INFORMATION

15. METHOD OF EQUIPMENT PAYMENT
a ☐ Rental b ☐ Purchase

16. TOTAL PURCHASE PRICE $________

17. PURCHASE OR RENTAL MONTHLY CHARGE $________

18. INSTALLATION CHARGE $________

19. DISPOSABLE SUPPLIES $________

20. CHANGES IN USUAL DIALYSIS SETTING *(If there has been a change in the patient's treatment plan such that he/she now has a new usual or regular treatment setting, indicate both the previous and the new setting by checking the appropriate "FROM" and "TO" columns below).*

DIALYSIS SETTING	FROM	TO
Outpatient-Full care	a ☐	b ☐
Outpatient-Partial care	c ☐	d ☐
Outpatient-Self-care	e ☐	f ☐
Outpatient-Self-care training	g ☐	h ☐
Home-Self-care	i ☐	j ☐
Home-Partial care	k ☐	l ☐

21. REASON(S) FOR CHANGE IN USUAL DIALYSIS SETTING *(Check all applicable reasons for change indicated in Item 20).*

a ☐ Medical complications
b ☐ Self-care training initiated
c ☐ Self-care training successfully completed
d ☐ Patient unable to complete training
e ☐ Change in home support
f ☐ Patient refuses to continue in present setting
g ☐ Other

22. REASON(S) FOR TEMPORARY DIALYSIS SETTINGS *(Check below all reasons for any dialysis treatments indicated in Item 12 which were given in a temporary setting; i.e., not the patient's usual setting).*

a ☐ Medical complications
b ☐ Change in home support
c ☐ Mechanical failure of equipment
d ☐ Patient on personal or job-related travel
e ☐ Patient or assistant temporarily unable to complete training
f ☐ Patient receiving additional self-care training
g ☐ Patient waiting for availability of space in another facility
h ☐ Other

23. CURRENT DIALYSIS PRESCRIPTION *(Usual setting)*
________ Hours per session

24. TYPE OF DIALYSIS *(Check one)*
a ☐ Hemodialysis only
b ☐ Peritoneal dialysis only
c ☐ Both *(Indicate number of treatments).*
________ Hemodialysis
________ Peritoneal dialysis

25. NUMBER OF DIALYSIS ACCESS PROCEDURES *(New or revised)* DURING THIS PERIOD *(Check none or enter number).*
a ☐ None
b __ Vascular
c __ Peritoneal

26. NUMBER OF UNITS OF BLOOD GIVEN THIS PERIOD *(Enter number of units given of each type. If number of units is unknown, enter "X" in appropriate category).*
a ☐ None
b ______ Frozen
c ______ Leukocyte poor *(Buffy coat free)*
d ______ Other
e ______ Unknown type

27. PATIENT TREATMENT STATUS *(Check one)*
a ☐ Dialysis only; not a transplant candidate
b ☐ Transplant candidate
c ☐ Transplanted, off dialysis
d ☐ Transplanted, on support dialysis
e ☐ Expired __ __ | __ __ | __ __ Mo. Day Yr.

28. REMARKS

NOTE: *If patient residence is not in a specific county, enter incorporated city or township.

This report is required by law (42. U.S.C. 426; 20 CFR 405, Section 2133). Individually identifiable patient information will not be disclosed except as provided for in the Privacy Act of 1974 (5 U.S.C. 5520; 45 CFR Part 5a).

Form SSA—2743 (10-76) SSA/ESRD Department of Health, Education, and Welfare

The Inpatient Hospital and Skilled Nursing Facility Admission and Billing form, SSA-1453 (figure 4-3), is submitted to fiscal intermediaries for reimbursement of services rendered. Information from this form is sent to the ESRD MIS through the Medicare masterfile.

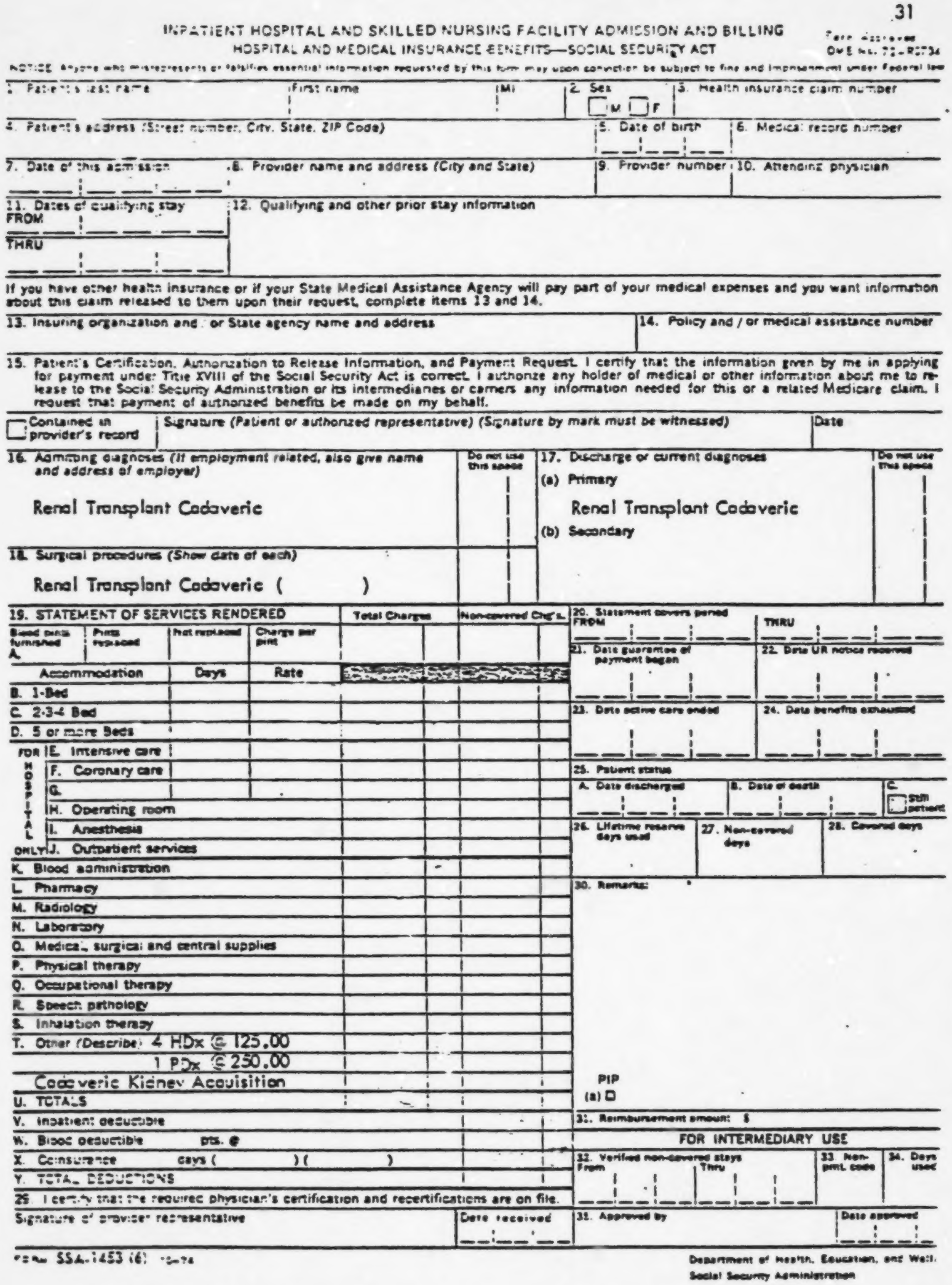
Transplant Tissue Typing Information (figure 4-4) is submitted within two weeks from the date of transplant.

A Death Notification (figure 4-5) is submitted when a death has occurred, regardless of the place or cause of death.

Compliance was a major problem within the system as it existed from 1977 to 1979. Information requested by HCFA for the ESRD MIS was not required by the Social Security Administration in order to receive Medicare benefits. If bills were submitted to SSA for a patient, they were paid, regardless of whether or not a Patient History and Treatment Plan had been submitted to HCFA.

The ESRD MIS management at HCFA had asked that the fiscal intermediaries police the system by requiring that a Patient History and Treatment Plan be submitted for each patient prior to the intermediaries' payment of the first bill. This procedure was in effect until two years ago. Unfortunately, it became unwieldy and impractical.

Until January 1981, supplemental forms were sent in with bills by intermediary or carrier. Communication between the intermediaries is poor and this creates additional data problems. For example, an intermediary would handle one State in which a patient lived; another intermediary would be responsible for the contiguous State in which the patient was dialyzed. The MIS is dependent on the intermediary to supply specific information that may or may not be accurate. The intermediary pays on the basis of the bill. They may adjust this payment, if there is a change, but do not take the time to adjust the supplemental document. Billing records are maintained separately from a patient's medical record.



INPATIENT HOSPITAL AND SKILLED NURSING FACILITY ADMISSION AND BILLING
HOSPITAL AND MEDICAL INSURANCE BENEFITS—SOCIAL SECURITY ACT

Form Approved
OMB No. 72-R0734

NOTICE: Anyone who misrepresents or falsifies essential information requested by this form may upon conviction be subject to fine and imprisonment under Federal law

1. Patient's last name | First name | MI
2. Sex ☐ M ☐ F
3. Health insurance claim number
4. Patient's address (Street number, City, State, ZIP Code)
5. Date of birth
6. Medical record number
7. Date of this admission
8. Provider name and address (City and State)
9. Provider number
10. Attending physician
11. Dates of qualifying stay FROM / THRU
12. Qualifying and other prior stay information

If you have other health insurance or if your State Medical Assistance Agency will pay part of your medical expenses and you want information about this claim released to them upon their request, complete items 13 and 14.

13. Insuring organization and / or State agency name and address
14. Policy and / or medical assistance number

15. Patient's Certification, Authorization to Release Information, and Payment Request. I certify that the information given by me in applying for payment under Title XVIII of the Social Security Act is correct. I authorize any holder of medical or other information about me to release to the Social Security Administration or its intermediaries or carriers any information needed for this or a related Medicare claim. I request that payment of authorized benefits be made on my behalf.

☐ Contained in provider's record | Signature (Patient or authorized representative) (Signature by mark must be witnessed) | Date

16. Admitting diagnoses (If employment related, also give name and address of employer)

Renal Transplant Cadaveric

Do not use this space

17. Discharge or current diagnoses

(a) Primary

Renal Transplant Cadaveric

(b) Secondary

Do not use this space

18. Surgical procedures (Show date of each)

Renal Transplant Cadaveric (   )

19. STATEMENT OF SERVICES RENDERED

				Total Charges	Non-covered Chg's.
Blood pints furnished A.	Pints replaced	Not replaced	Charge per pint		
Accommodation		Days	Rate		
B. 1-Bed					
C. 2-3-4 Bed					
D. 5 or more Beds					
FOR HOSPITAL ONLY	E. Intensive care				
	F. Coronary care				
	G.				
	H. Operating room				
	I. Anesthesia				
	J. Outpatient services				
K. Blood administration					
L. Pharmacy					
M. Radiology					
N. Laboratory					
O. Medical, surgical and central supplies					
P. Physical therapy					
Q. Occupational therapy					
R. Speech pathology					
S. Inhalation therapy					
T. Other (Describe) 4 HDx @ 125.00					
1 PDx @ 250.00					
Cadaveric Kidney Acquisition					
U. TOTALS					
V. Inpatient deductible					
W. Blood deductible pts. @					
X. Coinsurance days ( )( )					
Y. TOTAL DEDUCTIONS					

20. Statement covers period FROM / THRU
21. Date guarantee of payment began
22. Date UR notice received
23. Date active care ended
24. Date benefits exhausted
25. Patient status
A. Date discharged | B. Date of death | C. ☐ Still patient
26. Lifetime reserve days used
27. Non-covered days
28. Covered days
30. Remarks:

PIP
(a) ☐

31. Reimbursement amount: $

FOR INTERMEDIARY USE

32. Verified non-covered stays From / Thru
33. Non-pmt. code
34. Days used

29. I certify that the required physician's certification and recertifications are on file.

Signature of provider representative | Date received

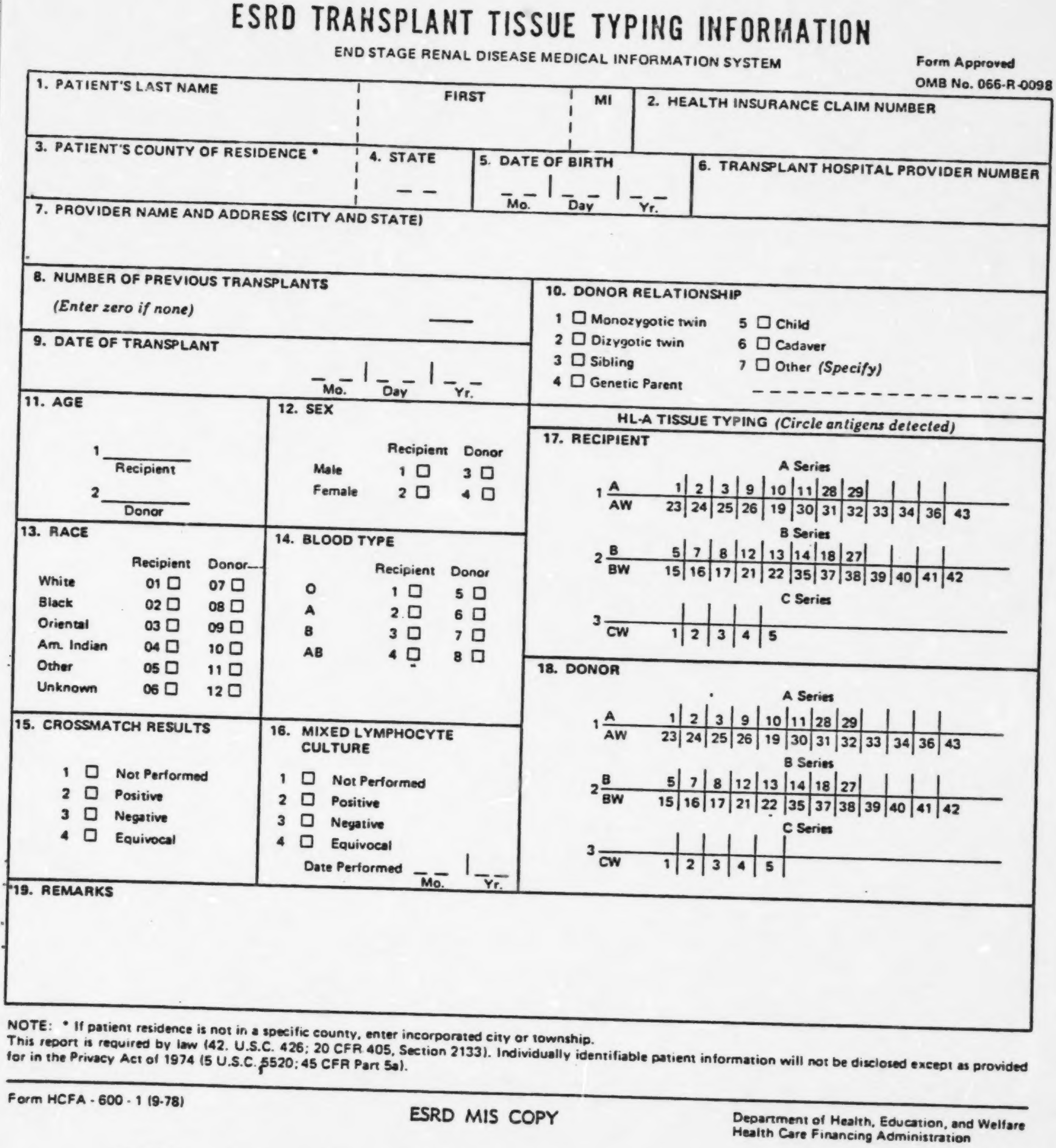
35. Approved by | Date approved

Form SSA-1453 (6) 10-74

Department of Health, Education, and Welfare
Social Security Administration

NOTE: This is an incomplete bill. Data entries are for example only.

FIGURE 4-3. INPATIENT HOSPITAL AND SKILLED NURSING FACILITY ADMISSION AND BILLING.



ESRD TRANSPLANT TISSUE TYPING INFORMATION

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM

Form Approved
OMB No. 066-R-0098

1. PATIENT'S LAST NAME | FIRST | MI

2. HEALTH INSURANCE CLAIM NUMBER

3. PATIENT'S COUNTY OF RESIDENCE *

4. STATE _ _

5. DATE OF BIRTH _ _ | _ _ | _ _ Mo. Day Yr.

6. TRANSPLANT HOSPITAL PROVIDER NUMBER

7. PROVIDER NAME AND ADDRESS (CITY AND STATE)

8. NUMBER OF PREVIOUS TRANSPLANTS
(Enter zero if none) ____

9. DATE OF TRANSPLANT _ _ | _ _ | _ _ Mo. Day Yr.

10. DONOR RELATIONSHIP

1 ☐ Monozygotic twin	5 ☐ Child
2 ☐ Dizygotic twin	6 ☐ Cadaver
3 ☐ Sibling	7 ☐ Other *(Specify)* ________
4 ☐ Genetic Parent	

11. AGE

1 ________ Recipient

2 ________ Donor

12. SEX

	Recipient	Donor
Male	1 ☐	3 ☐
Female	2 ☐	4 ☐

13. RACE

	Recipient	Donor
White	01 ☐	07 ☐
Black	02 ☐	08 ☐
Oriental	03 ☐	09 ☐
Am. Indian	04 ☐	10 ☐
Other	05 ☐	11 ☐
Unknown	06 ☐	12 ☐

14. BLOOD TYPE

	Recipient	Donor
O	1 ☐	5 ☐
A	2 ☐	6 ☐
B	3 ☐	7 ☐
AB	4 ☐	8 ☐

15. CROSSMATCH RESULTS

1 ☐ Not Performed
2 ☐ Positive
3 ☐ Negative
4 ☐ Equivocal

16. MIXED LYMPHOCYTE CULTURE

1 ☐ Not Performed
2 ☐ Positive
3 ☐ Negative
4 ☐ Equivocal
Date Performed _ _ | _ _ Mo. Yr.

HL-A TISSUE TYPING *(Circle antigens detected)*

17. RECIPIENT

A Series

1 A	1	2	3	9	10	11	28	29				
AW	23	24	25	26	19	30	31	32	33	34	36	43

B Series

2 B	5	7	8	12	13	14	18	27				
BW	15	16	17	21	22	35	37	38	39	40	41	42

C Series

3 CW	1	2	3	4	5

18. DONOR

A Series

1 A	1	2	3	9	10	11	28	29				
AW	23	24	25	26	19	30	31	32	33	34	36	43

B Series

2 B	5	7	8	12	13	14	18	27				
BW	15	16	17	21	22	35	37	38	39	40	41	42

C Series

3 CW	1	2	3	4	5

19. REMARKS

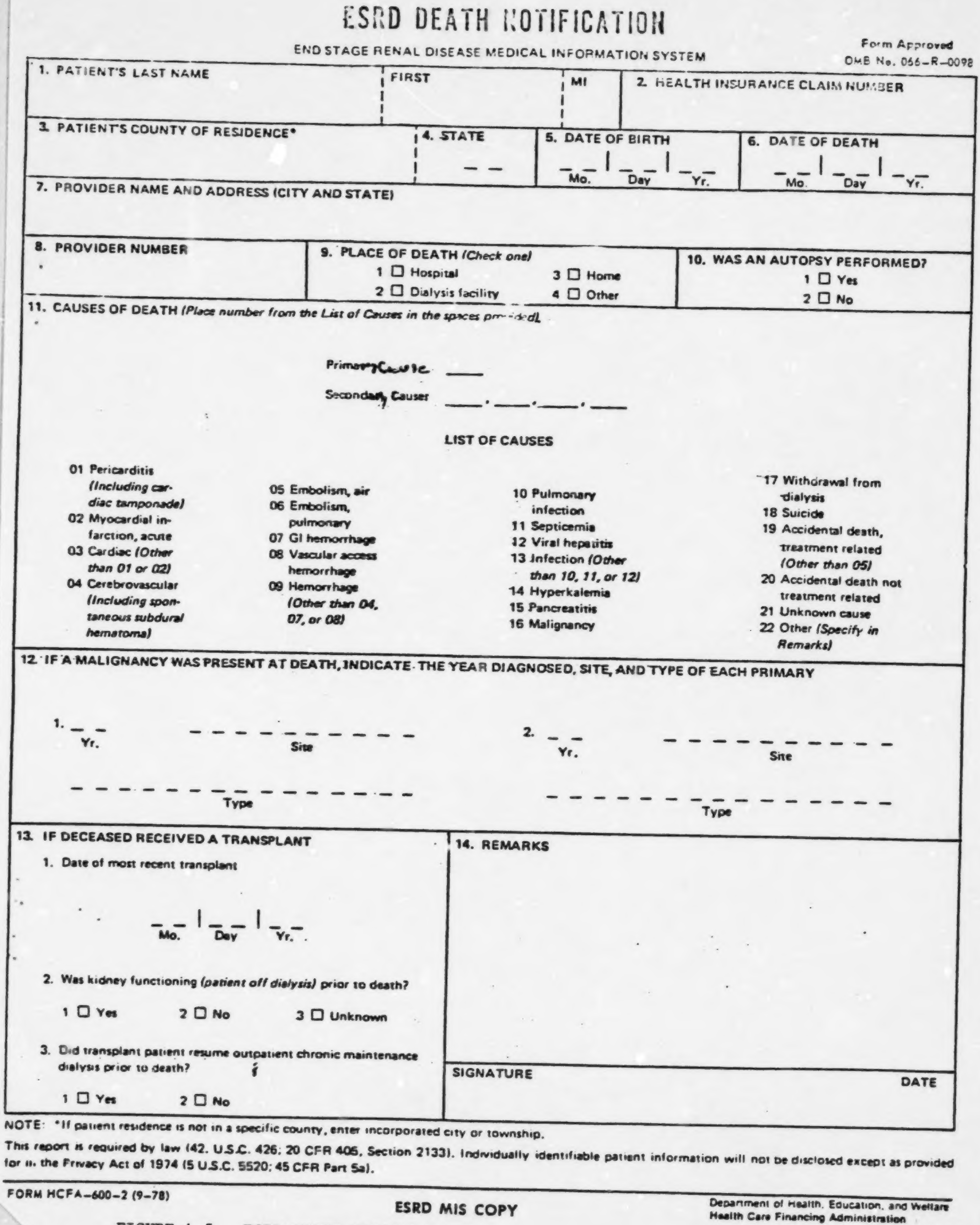
NOTE: * If patient residence is not in a specific county, enter incorporated city or township.
This report is required by law (42. U.S.C. 426; 20 CFR 405, Section 2133). Individually identifiable patient information will not be disclosed except as provided for in the Privacy Act of 1974 (5 U.S.C. 5520; 45 CFR Part 5a).

Form HCFA - 600 - 1 (9-78)

ESRD MIS COPY

Department of Health, Education, and Welfare
Health Care Financing Administration

FIGURE 4 -4. ESRD TRANSPLANT TISSUE TYPING INFORMATION.



ESRD DEATH NOTIFICATION

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM

Form Approved
OMB No. 066–R–0098

1. PATIENT'S LAST NAME | **FIRST** | **MI** | **2. HEALTH INSURANCE CLAIM NUMBER**

3. PATIENT'S COUNTY OF RESIDENCE* | **4. STATE** __ __ | **5. DATE OF BIRTH** __ __ | __ __ | __ __ Mo. Day Yr. | **6. DATE OF DEATH** __ __ | __ __ | __ __ Mo. Day Yr.

7. PROVIDER NAME AND ADDRESS (CITY AND STATE)

8. PROVIDER NUMBER

9. PLACE OF DEATH *(Check one)*
1 ☐ Hospital
2 ☐ Dialysis facility
3 ☐ Home
4 ☐ Other

10. WAS AN AUTOPSY PERFORMED?
1 ☐ Yes
2 ☐ No

11. CAUSES OF DEATH *(Place number from the List of Causes in the spaces provided).*

Primary Cause ____

Secondary Causes ____, ____, ____, ____

LIST OF CAUSES

- 01 Pericarditis *(Including cardiac tamponade)*
- 02 Myocardial infarction, acute
- 03 Cardiac *(Other than 01 or 02)*
- 04 Cerebrovascular *(Including spontaneous subdural hematoma)*
- 05 Embolism, air
- 06 Embolism, pulmonary
- 07 GI hemorrhage
- 08 Vascular access hemorrhage
- 09 Hemorrhage *(Other than 04, 07, or 08)*
- 10 Pulmonary infection
- 11 Septicemia
- 12 Viral hepatitis
- 13 Infection *(Other than 10, 11, or 12)*
- 14 Hyperkalemia
- 15 Pancreatitis
- 16 Malignancy
- 17 Withdrawal from dialysis
- 18 Suicide
- 19 Accidental death, treatment related *(Other than 05)*
- 20 Accidental death not treatment related
- 21 Unknown cause
- 22 Other *(Specify in Remarks)*

12. IF A MALIGNANCY WAS PRESENT AT DEATH, INDICATE THE YEAR DIAGNOSED, SITE, AND TYPE OF EACH PRIMARY

1. __ __ Yr. ____________ Site ____________ Type
2. __ __ Yr. ____________ Site ____________ Type

13. IF DECEASED RECEIVED A TRANSPLANT

1. Date of most recent transplant
__ __ | __ __ | __ __
Mo. Day Yr.

2. Was kidney functioning *(patient off dialysis)* prior to death?
1 ☐ Yes 2 ☐ No 3 ☐ Unknown

3. Did transplant patient resume outpatient chronic maintenance dialysis prior to death?
1 ☐ Yes 2 ☐ No

14. REMARKS

SIGNATURE **DATE**

NOTE: *If patient residence is not in a specific county, enter incorporated city or township.

This report is required by law (42. U.S.C. 426; 20 CFR 405, Section 2133). Individually identifiable patient information will not be disclosed except as provided for in the Privacy Act of 1974 (5 U.S.C. 5520; 45 CFR Part 5a).

FORM HCFA–600–2 (9–78)

ESRD MIS COPY

Department of Health, Education, and Welfare
Health Care Financing Administration

FIGURE 4-5. ESRD DEATH NOTIFICATION.

4.1.2 The ESRD MIS Patient Population

Only those eligible for Medicare benefits are included in the ESRD MIS. This excludes certain groups such as veterans, Federal employees, and the persons without sufficient earnings to be eligible for social security benefits. These groups comprise, perhaps, 10 percent of the entire end stage renal disease patient population in the United States. Consequently, only 90 percent of the ESRD patient population is eligible for inclusion in the ESRD MIS.

Two groups of patients constitute the ESRD MIS patient population. In-unit patients are those patients who are treated in a facility either with hemodialysis, peritoneal dialysis, or both. In-home patients are those treated at home. In-home patients account for 13 percent of the end stage renal disease patient population. It is assumed that they also account for 13 percent of the ESRD MIS patient population.

It is not known whether these in-home patients are on hemodialysis, peritoneal dialysis, or continuous ambulatory peritoneal dialysis (CAPD). ESRD MIS data from 1973 to the present confirm only that the patient is receiving service at home, but not the type of service received. This is because cost information concerning supplies is listed, but information as to type of supplies is not requested. The type of dialysis listed in the database is the type of treatment received when home treatment begins. If the type of dialysis treatment changes, the change may not be reported.

Continuous ambulatory peritoneal dialysis (CAPD) patients are not identified, as such, whether in-home or in-facility. Prior to September 1979, CAPD was not recognized as an authorized treatment modality and was not paid for by Medicare. Therefore, whatever authorized treatment modality the patient started on continued to be listed in the ESRD MIS data base. If a patient started treatment on hemodialysis and then switched to CAPD, treatment remained listed as hemodialysis. If a patient began treatment on CAPD, it would be listed as peritoneal dialysis or hemodialysis to obtain Medicare subsidies. Beginning in April 1981, ESRD MIS will be modified to recognize and pick up CAPD patients.

An additional problem with the dataset is that the patients listed may or may not be end stage renal disease patients. Several explanations are offered for this problem.

One explanation is that service providers initially assumed that a Patient History and Treatment Plan should be submitted to HCFA if a patient ever received dialysis. Because of this belief, acutely ill patients, requiring short-term dialysis, were often required to fill out the form and were introduced into the system data base.

Another difficulty is that the first design of the Patient History and Treatment Form was entitled "Medicare Patient History." This title led many patients already enrolled in Medicare, but not on dialysis, to complete and submit this form. These forms were routinely entered into the system data base.

Consequently, HCFA does not know what percentage of the approximately 6,000 questionable patients included in the dataset were ever actually dialyzed, and what percentage are "legitimate" long-term dialysis patients. These erroneous records are currently being cleared off the system database by HCFA.

4.1.3 The ESRD Patient History and Treatment Plan

Limited medical information is included in the ESRD MIS. The Patient History and Treatment Plan contains the following data elements:

- Patient name
- Sex
- Health insurance claim number, name, and address
- Intermediary number
- Race (entered by observation only).

All identifiers, such as patient name, health insurance number, provider number, name and address, and the intermediary number were deleted from the dataset. HCFA believes the remaining patient demographic data provided are reliable. The medical information included primary disease, methods of diagnostic confirmation, complicating conditions which are or were present, and surgical and transplant histories.

Completeness

The History and Treatment Plan is the only form that provides information concerning cause of end stage renal disease. Unfortunately, these data are not updated. As mentioned earlier, the only instance where a second history is submitted occurs when a patient requires additional dialysis after a "successful" transplant rejects and the patient therefore re-enters the system. Transplants occuring between July 1973 and October 1977 were considered successful if the patient remained off dialysis for a period of 12 months. After the 12-month point, Medicare benefits were terminated and no additional patient records were supplied to the system data base. Because 12 months has been found to be too short a period for tracking transplant patients, HCFA has modified the entitlement policy so that transplant patients are now followed for a 36-month period.

Another problem is that transplants before 1973 are not known. If a pre-1973 transplant patient rejects and requires a return to dialysis, the date of first chronic maintenance dialysis entered on the Patient History and Treatment Plan will most likely be listed as the date of return to treatment, rather than the date of treatment initiation preceding transplant.

If a complicating medical condition develops while the patient is undergoing dialysis, that information is rarely captured. The only instance in which such a complication would be routinely identified occurs if: the condition occasions the admission of the patient to a hospital or a skilled nursing facility, and the complicating condition is listed on the bill (Form SSA-1453) as the principal or secondary diagnosis. A second instance in which a complicating medical condition, that develops after dialysis is initiated, might be picked up occurs when a patient dies. If a Death Notification (Form HCFA-600-2) is submitted, it may or may not list--as a primary or secondary cause of death--a condition which developed subsequent to completion of the

History and Treatment Plan. This must be considered an unreliable collection mechanism.

Additional data include:

- Date of first chronic maintenance dialysis
- Highest serum creatinine level prior to first dialysis
- Present dialysis access
- Patient treatment classification
- If the patient is not a transplant candidate, the reasons why.

The planned dialysis modality and treatment setting are requested. If the patient is not planned for home dialysis, an explanation is requested. The patient's current health status (level of activity) and employment status also are recorded.

Since it is not required to receive Medicare benefits, often the Patient History and Treatment form is not submitted to HCFA. In 1978, the percent of new patients not submitting forms, by network, ranged from a low of 26 percent unreported in one network to a high of 87 percent unreported in another, with a nationwide average of 53 percent not submitting this report.

Accuracy

Without identifying patients and reviewing individual medical records, many of the fields on the Patient History and Treatment Plan are unreliable. The medical information that is requested is limited and the accuracy of the responses obtained is questionable.

If the patient has had a malignancy or if a malignancy is currently present, the year diagnosed, site, and type of each primary malignancy is requested. According to Dr. Joseph Fraumeni, Jr., of the National Cancer Institute, Environmental Epidemiology Branch, these data are considered unreliable. To be considered valid, the information must be verified by reference to individual medical records. It is possible to ascertain, with some degree of confidence, the population's age, sex, and race. The fact of dialysis and the type of dialysis is fairly reliable, though there are problems with these figures due to the inability to report CAPD patients, and the in-home patient factor.

It would be necessary to review individual medical records in order to determine anything as specific as medications the patient is receiving, patient smoking and alcohol history, cause of end stage renal disease for many, and complicating conditions present for many more. It would also be necessary to review medical records to validate presence and type of malignancy with any degree of accuracy. The date of first chronic maintenance dialysis is also a questionable data field, since pre-1973 transplants were not reported.

4.1.4 The ESRD Outpatient Dialysis Service Information

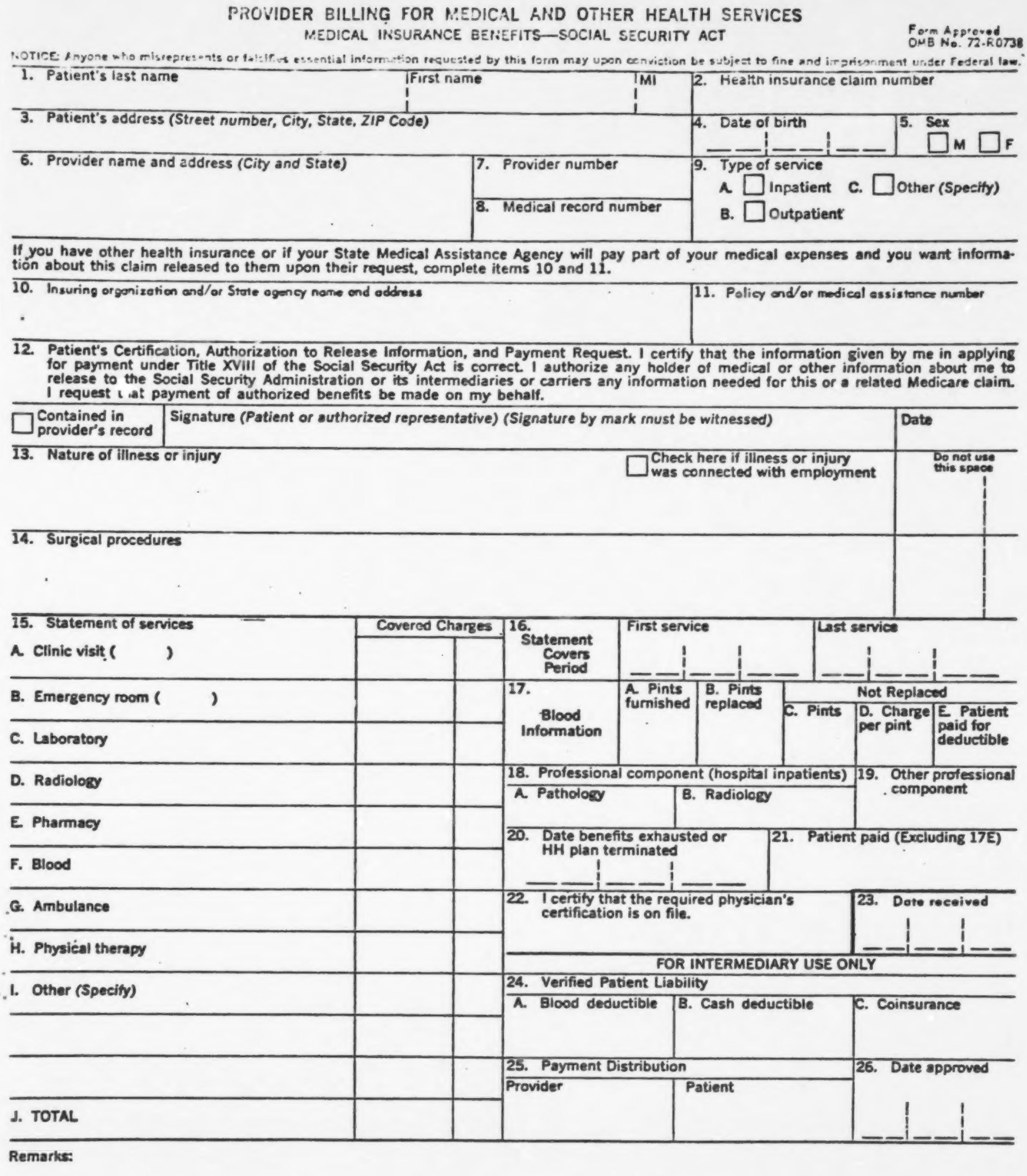
The ESRD MIS Outpatient Dialysis Service Information is completed at the close of each billing period and is attached to the Provider Billing for Medical and Other Health Services (Form SSA-1483), shown in figure 4-6. Information requested, in addition to patient and provider identifying data, includes:

- Dialysis setting (outpatient or home) and number of sessions
- Changes in the usual dialysis setting
- Reason(s) for change
- Reason(s) for temporary dialysis settings.

The number of sessions is used in calculating the change. Medicare will pay for 39 treatment sessions per month. If more than 39 sessions are indicated, the Medicare intermediary will review the medical record before determining payment.

Accuracy

The average number of sessions reported is 31; however, this field is not considered reliable. It is felt that, while the bill is accurate (what the intermediary bases payment on), intermediary payers make no effort to update



PROVIDER BILLING FOR MEDICAL AND OTHER HEALTH SERVICES
MEDICAL INSURANCE BENEFITS—SOCIAL SECURITY ACT

Form Approved
OMB No. 72-R0738

NOTICE: Anyone who misrepresents or falsifies essential information requested by this form may upon conviction be subject to fine and imprisonment under Federal law.

1. Patient's last name	First name	MI	2. Health insurance claim number
3. Patient's address (Street number, City, State, ZIP Code)		4. Date of birth	5. Sex ☐ M ☐ F
6. Provider name and address (City and State)	7. Provider number 8. Medical record number		9. Type of service A. ☐ Inpatient C. ☐ Other (Specify) B. ☐ Outpatient

If you have other health insurance or if your State Medical Assistance Agency will pay part of your medical expenses and you want information about this claim released to them upon their request, complete items 10 and 11.

10. Insuring organization and/or State agency name and address	11. Policy and/or medical assistance number

12. Patient's Certification, Authorization to Release Information, and Payment Request. I certify that the information given by me in applying for payment under Title XVIII of the Social Security Act is correct. I authorize any holder of medical or other information about me to release to the Social Security Administration or its intermediaries or carriers any information needed for this or a related Medicare claim. I request that payment of authorized benefits be made on my behalf.

☐ Contained in provider's record	Signature (Patient or authorized representative) (Signature by mark must be witnessed)	Date
13. Nature of illness or injury	☐ Check here if illness or injury was connected with employment	Do not use this space
14. Surgical procedures		

15. Statement of services	Covered Charges		
A. Clinic visit ( )			16. Statement Covers Period — First service — Last service
B. Emergency room ( )			17. Blood Information — A. Pints furnished — B. Pints replaced — Not Replaced: C. Pints — D. Charge per pint — E. Patient paid for deductible
C. Laboratory			
D. Radiology			18. Professional component (hospital inpatients) — A. Pathology — B. Radiology — 19. Other professional component
E. Pharmacy			
F. Blood			20. Date benefits exhausted or HH plan terminated — 21. Patient paid (Excluding 17E)
G. Ambulance			22. I certify that the required physician's certification is on file. — 23. Date received
H. Physical therapy			FOR INTERMEDIARY USE ONLY
I. Other (Specify)			24. Verified Patient Liability — A. Blood deductible — B. Cash deductible — C. Coinsurance
			25. Payment Distribution — Provider — Patient — 26. Date approved
J. TOTAL			

Remarks:

FIGURE 4-6. PROVIDER BILLING FOR MEDICAL AND OTHER HEALTH SERVICES.

FORM SSA-1483 (1-73)

Department of Health, Education, and Welfare
Social Security Administration

the supplemental information. Consequently, HCFA believes that a relatively fixed number of sessions is reported for each patient, regardless of actual changes in treatment activity.

Since the current dialysis prescription is specified on the outpatient form, this figure should represent the average number of hours per dialysis session that patients were dialyzed in their current setting. However, this field is usually not filled in correctly and HCFA believes that the original prescription is entered repeatedly month after month. If the prescription has changed, it may be noted in the patient's medical record, but not changed in the patient's billing record. There is no way to edit this field for correctness; consequently, it will be eliminated from the ESRD MIS data base as of April 1981.

An additional problem in this area involves the hours dialyzed per session, which in practice vary greatly from session to session. If patients have consumed alcohol or more than their usual amount of fluids, they will need to be dialyzed longer. The only way to obtain accurate information as to length of individual treatment sessions is to consult individual patient medical records.

Additional outpatient dialysis information collected includes the type of dialysis. On in-unit patients, this information is probably fairly accurate. But, as discussed earlier, if a home patient has changed dialysis methods, this information will not be picked up. Information concerning the number of dialysis access procedures during each monthly reporting period, the number of units of blood given during this period, and the patient's current treatment status is also collected. Though the Outpatient Dialysis Service Information form is usually submitted, it is often inaccurate because it is not updated.

4.1.5 The ESRD Transplant Tissue Typing Information

The ESRD Transplant Tissue Typing Information (Form HCFA-600-1) provides transplant data. Information concerning transplants prior to 1973 was not collected.

Unreported forms are a problem in gaining this information. In 1978, the percent unreported, by network, ranged from a low of 30 percent unreported in one network to a high of 100 percent unreported in another, creating a nationwide average of 42 percent unreported transplants.

4.1.6 The ESRD Death Notification

The ESRD Death Notification (Form HCFA-600-2) contains identifying data, date and place of death, and whether or not an autopsy was performed. Primary and secondary causes of death also are collected. If a malignancy was present at death, the year diagnosed, site, and type of each primary malignancy is requested.

If the deceased received a transplant, information as to date of most recent transplant, whether the kidney was functioning prior to death, and whether the patient resumed outpatient chronic maintenance dialysis prior to death is requested. This form was implemented only in 1977.

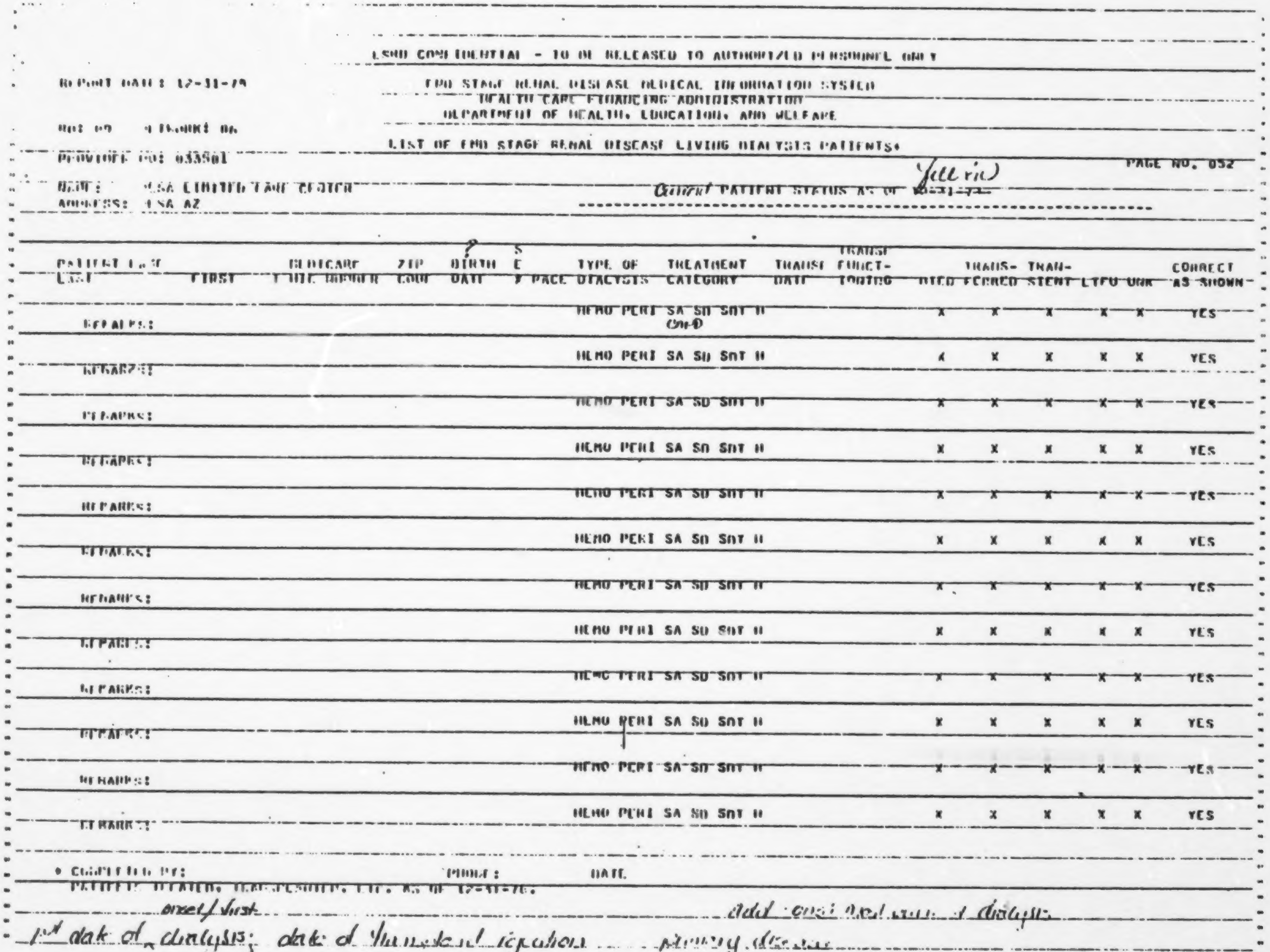
In 1978, the national average for unreported Death Notification was 68 percent. The percent unreported, by network, ranged from a low of 19 percent to a high of 85 percent. While the fact of death is known, the cause of death is known for an average of only 32 percent of the population. Some additional causes of death could be collected, if an end stage renal disease patient died in a hospital and the cause of death was the reason for admission. Consequently, this is an unreliable collection mechanism.

Additional data reported on this form, such as malignancy information, would have to be verified from the individual patient medical record to be considered reliable.

4.1.7 The ESRD Center Patient Listing

The ESRD Center Patient Listing (figure 4-7) was provided without identifiers, so this additional information could only be considered as reliable as the data listed on the other input documents, since it is a compilation of these documents.

FIGURE 4-7. ESRD CENTER PATIENT LISTING.



ESRD CONFIDENTIAL - TO BE RELEASED TO AUTHORIZED PERSONNEL ONLY

REPORT DATE: 12-31-79

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM
HEALTH CARE FINANCING ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NOT 09 [illegible]

LIST OF END STAGE RENAL DISEASE LIVING DIALYSIS PATIENTS*

PROVIDER NO: 033501

PAGE NO. 052

NAME: USA LIMITED CARE CENTER
ADDRESS: USA AZ

(fill in)
Current PATIENT STATUS AS OF ~~12-31-79~~

PATIENT NAME LAST	FIRST	MEDICARE CLAIM NUMBER	ZIP CODE	? BIRTH DATE	SEX	RACE	TYPE OF DIALYSIS	TREATMENT CATEGORY	TRANSF DATE	TRANSP FUNCT-IONING	DIED	TRANS-FERRED	TRAN-SIENT	LTFU	UNK	CORRECT AS SHOWN
REMARKS:							HEMO PERI	SA SD SDT H Con-D			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES
REMARKS:							HEMO PERI	SA SD SDT H			X	X	X	X	X	YES

* COMPLETED BY: PHONE: DATE
PATIENTS TREATED, [illegible], ETC. AS OF 12-31-79.

onset/first add: onset [illegible] of dialysis
1st date of dialysis; date of transplant rejection primary disease

4.1.8 The ESRD Facility Cost Questionnaire

The Facility Cost Questionnaire, which during the 1970s was completed annually, is the only document in the MIS that contains any type of information concerning types of machines and reuse of coils. Since June 1980, the Facility Cost Questionnaire has been completed semi-annually.

The questionnaire is designed to provide a limited amount of information. Specific information relating to machine use includes:

- Number of fixed-position and portable machines
- Number of coil and parallel flow machines
- Information on whether coils are reused and, if they are, how often (on the average).

In order to determine anything as specific as brands of machines, types of membranes, amount of tubing, treatment of water, and sterilants used, it would be necessary to contact individual facilities.

4.1.9 Problems with the ESRD MIS Data: A Summary

The various elements reported in the ESRD MIS have decreasing reliabilities. Age, sex, and race data are reliable. Information concerning primary cause of disease, complicating conditions, and malignancies is not very reliable. To get reliability, it would be necessary to verify these data by reviewing individual patient medical records. Fact and type of dialysis is fairly reliable, although, as stated earlier, problems exist with these figures.

Fact of death is known, but cause of death, when identified, would need to be verified by reviewing patient medical records. Patient and provider identifiers were not specified, thus making it impossible to return to individual medical records.

Poor compliance in reporting to the ESRD MIS presents a major problem. According to HCFA, the percentage of unreported forms increases with each previous year of operation. JRB was provided with 1978 figures. Consequently, it is likely that a higher percentage of unreported forms occurred in 1977. Reporting rates may have improved slightly for 1979, and HCFA believes they are continuing to improve.

The data available in the ESRD MIS, as it existed during the years 1977 through 1979, are limited and must be qualified. Poor compliancy rates and inaccurate reporting are major factors that must be considered. In addition, sufficient detail is not collected by the ESRD MIS. The information necessary to conduct an epidemiologic study is not available through the ESRD MIS alone.

4.2 ASSESSMENT OF EPIDEMIOLOGIC RESEARCH POTENTIAL OF ESRD MIS DATA

In the determination of causality, the relevant competing factors to which the selected population is exposed were identified:

- Copper and zinc from the filtration membranes, the component action of which causes leukopenia and hypoxia. In addition, the trace element of cadmium, a carcinogen, is a contaminant of zinc and copper compounds.
- Sterilizing agents, such as formaldehyde, that have been directly correlated with hemolysis and recently have been shown to cause cancer in test animals.
- Water used in dialysate and containing fluoride, which has been demonstrated to produce bone disease.
- Chloramine, which causes hemolysis.
- Nitrate-nitrite, which also is linked with hemolysis and other synergistic effects.
- Heparin, which is linked to the development of ostopenia.

4.2.1 Specificity

The Patient History and Treatment Plan provides medical information on the first day of treatment, primary cause of ESRD, complicating conditions, type of dialysis, method of diagnosis, dialysis access, surgical history, and history of malignancy, in addition to relevant demographic information. For the most part, information of this type would not be specific enough to draw conclusions as to the extent of the condition, the severity of the condition, and the impact of the condition on the constitutional factors of the patient.

Medical information available from the ESRD Outpatient Service Information form includes type of dialysis, setting for dialysis treatment, reasons for selection of dialysis setting used, and current dialysis prescription. Again, the specificity of the information is limited to checking the type of modality, which for the home-dialysis population is not fully known, and the prescription, which can provide only approximate information as to how long and how many treatments a patient received. However, the form does not include the type of medications used, the additions of concentrate to the dialysate, or information relating to any changes in the composition of the dialysate, itself.

The reason for change of setting does specify "medically unfit" as a factor for selection of dialysis setting, but does not provide information on the type of medical complication, the severity of the condition, whether the condition is acute or chronic, or if it is associated with end stage renal disease or an accompanying concomitant disease.

Medical information from the ESRD Death Notification provides primary and secondary causes of death, if an autopsy was performed, transplant information, and information on malignancy. Information recorded provides the "fact of" these variables, but does not provide information specific enough to describe the factors which precipitated the events listed or the outcomes of these events.

4.2.2 Accuracy

The Health Care Financing Administration has supplied information pertaining to the accuracy of the data within the ESRD MIS. It is HCFA's belief that information pertaining to the demographic characteristics (age, sex, race), date of initial chronic maintenance dialysis treatment (with the exception of pre-1973 transplants), fact of dialysis, fact of death, fact of transplant, and type of dialysis is accurate. Information which they feel is greatly lacking in accuracy include:

- Cause of death
- Prescription data (number of hours of dialysis treatment), a field which is being removed from the system in April 1981
- Type of dialysis modality used by the home-treatment population
- Data pertaining to malignancy (both patient treatment and history and death notification).

Information pertaining to primary cause of end stage renal disease and complications must be verified by consulting the individual patient's medical records. Information pertaining to dose, needed to perform an analysis associating dose response to outcome, is unavailable, since prescription information is considered to be invalid. Since cause of death and malignancy data are considered to be unreliable without verification from medical records, there can be no basis for information pertaining to outcome. The ESRD MIS database records the prevalent conditions stated above; however, the ESRD MIS is not designed to collect information relating to incidence of disease during the treatment period, unless the condition requires hospitalization and in this case only billable information is captured. Therefore, adjustment from competing causes of death not specified in the Patient History and Treatment Plan cannot be accomplished.

4.2.3 Completeness

A major factor in determining the generalizability of research findings is the representativeness of the population data being analyzed. The ESRD MIS has had great difficulty in aquiring the compliance of the provider population. In 1978, the ESRD MIS received national averages of only 47 percent of initial Patient History and Treatment Plans, and only 32 percent of the Death Notification forms. Network compliance ranged from a high of 74 percent to a low of 13 percent for the Patient History and Treatment Plan form and 81 percent to 15 percent for the Death Notification form. In light of this, it will be extremely difficult to describe the study population in terms of representativeness.

4.2.4 Statistical Methodology

Many questions arise concerning the analysis of ESRD MIS data over and above the quality of the data, itself.

The salient characteristic of this dataset is that the patients are under different lengths of observation time, the duration dependent upon factors other than the event of interest, i.e., the development of a malignancy. This requires that the response variable not be a dichotomous either/or variable on the individual patient, hence not a prevalence rate for the treatment group.

The response variable here is time from first treatment to development of malignancy, and the methodology of failure time (survival) is applicable.

Since so many covariates must be adjusted for, it is clear that a multiple regression model is required. An assumption must be made about the underlying distribution of times to the event, and the justification for this assumption will influence the nature of the analysis and the outcome of the study: i.e., if exponential, can the hazard function be assumed to be constant over time? If a distribution-free method is used, such as proposed by Mantel (1966) or Cox (1972), then is the assumption of a constant relative risk over time justified? It would appear not, since the longer the exposure to hemodialysis, the greater the risk versus those on peritoneal dialysis.

Although the sample size is large, the number of covariates is potentially exceptionally large, and there are dangers associated with the estimation of many parameters by the maximum likelihood method used for these models. These techniques can produce inconsistent estimates which require careful investigation to assure that they are reasonable. Additional terms, the interactions, would also require investigation.

Some of the covariates could be time-dependent, and would require special treatment.

A basis would need to be established for assuming model effects were either additive or multiplicative.

How will the treatment groups be represented--each separately, hence by two dummy variables, or hemodialysis plus combined versus peritoneal dialysis, and why? What about the heterogeneity in the proportions of hemodialysis and peritoneal dialysis received by the individuals in the combined group?

Given the very large difference between the hemodialysis and the peritoneal dialysis groups in sample size, how will the contrast in the precision of their measurements be adjusted for?

Will the latency periods for the development of different types of malignancies be covered by the relatively short observation time on each patient?

Since the competitive risks of death from other diseases are very great in this study, how will they be adjusted for in the response measure of time to developed malignancy?

What will be done with observations containing missing data? Most of the applicable techniques of statistical analysis have no procedures for dealing with missing data. Will the final, cleaned-up dataset be truly representative of the population of interest, and equally representative of each treatment group individually?

4.2.5 Summary Conclusion

After considering the limitations of the dataset and carefully assessing the likelihood of fruitful results from future investigations along these lines of research, it was found that the ESRD MIS is not suitable for the type of analyses required to determine the additional risk to ESRD patients. This decision is based upon the following reasons:

- The quality of the data to be used, according to both the HCFA Branch Chief of ESRD MIS and Drs. Fraumeni and Hoover of NCI, lacks the accuracy, completeness, and consistency necessary to perform any meaningful clinical analysis.

- This type of analysis has the danger connected with "fishing": if enough testing is done, it is highly probable that some variables might correlate. However the validity of such findings will suffer from the inaccuracies of the data used to determine them.
- The understandable reluctance of the Health Care Financing Administration to provide ESRD MIS patient identifier data, which would be required to perform a future comprehensive epidemiologic investigation of the ESRD patient population.

As noted elsewhere in this volume, it is perhaps feasible to use end stage renal disease patients as an epidemiologic study population, if appropriate attention were to be devoted to addressing rigorously the complex of biomedical conditions and confounding factors represented by the pathological processes, treatment regimens, dialysis modalities, and multiple exposures involved. Useful information on some of the competing disease etiologies might result from such a study. But at the present time and with the knowledge and detection capabilities currently available, mortality or morbidity incidence attributable to DEHP exposure would not be a fruitful subject for such an investigation.

Furthermore, the End Stage Renal Disease Medical Information System data base does not offer an adequate route of approach to epidemiologic research on the patient population. HFCA program officials recognize and concur in this judgment. The dataset provided offers the potential for demographic analysis, but very little beyond demographics.

If epidemiologic evidence of the health consequences of chronic exposure to DEHP is sought, it must be sought in a population less confounded than systemically ill end stage renal disease patients.

CHAPTER 5

AN EXAMINATION OF AN EPIDEMIOLOGICAL STUDY WITH ESRD PATIENTS

D. Wellington, Ph.D., and I. Marks, M.P.H.

A great many factors are involved in the development and treatment of end stage renal desease. An investigation of causality in populations with renal failure must include an examination of variables involved in the pathological processes. Close examination of these factors requires both an understanding of the disease and treatment, and the limitations inherent in uncontrolled field investigations. Evaluation of the factors associated with the ESRD population concludes that ESRD patients may not constitute a viable study group for an epidemiological investigation of the carcinogenic effect of exposure to DEHP for two reasons: 1) the inability to measure exposure to DEHP separately from exposure to carcinogens and possible etiologic factors; and 2) the extremely high combined competitive risk of mortality or morbidity from causes other than primary liver cancer and other malignancies.

The limitations of an epidemiologic study of ESRD patients include the multiple disease processes leading to chronic renal failure and the various treatments of renal disease which may, in themselves, lead to the development of primary liver cancer and other malignancies. This chapter discusses these causal factors, how they affect the design of an epidemiologic study of ESRD patients, and the problems associated with that design from an epidemiologic standpoint.

Renal failure leading to dialysis is not a single-entity disease. Renal failure is a trauma to the renal system resulting in irreversible damage. The therapeutic approach to the replacement of homeostatic functions usually provided by functioning kidneys is dialysis. Dialysis, without regard to the specific modality, presents multiple toxic factors, in addition to the disease, for which the body must compensate. It is feasible to envision the total force of ESRD mortality as simply the sum of interdependent competing factors.

Several aspects of the origin and natural history of chronic renal failure, or end stage renal disease, complicate an investigation of the determinants of another disease, such as cancer, in an ESRD patient population. These aspects include the multifactorial nature of etiology. End stage renal disease can occur from a pathologic process which affects the function of the kidneys, or as a secondary condition, resulting from such diseases as diabetic nephropathy or lupus erythematosus which may contribute to chronic renal failure. Each of these conditions has a particular affect on a number of body systems. The interaction of multiple conditions can be either additive or multiplicative, exacerbating other conditions or involving other systems which previously were functioning in a relatively normal manner. The multiplicity of these factors and their effects upon the development of disease vary between patients, making it increasingly difficult to assemble a population which meets a standard selection criteria.

Another aspect is the long latent period. End stage renal disease is a long and degenerative condition. Its natural history includes a great many pathologies which contribute to the progression of the disease and its complications. In such cases, it is difficult to link antecedent events to outcome.

The final aspect is the differential effect of factors on the incidence and course of the disease. Factors may act differently at various stages of the disease. For example, patients who suffer from end stage renal disease, and later develop diabetes as a result of aging and other factors not directly related to the primary renal failure, differ from patients who develop chronic renal failure as a result of a hypertensive condition caused by diabetes. Therefore, it is important when conducting a epidemiological study to differentiate between different stages and categories of disease to adjust for competing causes of morbidity and mortality.

5.1 The Problem of Causality in the ESRD Patient Population

The determination of causal associations can be obscured by a number of confounding variables. Therefore, a number of observational studies must be performed to establish proof of a causal relationship in any association.

Interpretation of such an association must be conducted in a systematic manner. The Advisory Committee to the Surgeon General, U.S. Public Health Service, defined five criteria that should be fulfilled to establish a causal relationship. These five criteria have been generally adopted as a test of causation:

- Consistency of association
- Strength of association
- Specificity of association
- Temporal relationship of association
- Coherence of association (Mausner et al. 1974).

The potential for obtaining each of these five criteria in the ESRD patient population is addressed in the following paragraphs.

Consistency of Association requires that an association determined in one study persist in testing under other circumstances, with other study populations, and in some cases, different countries. The more often the particular association appears under diverse circumstances, the more likely it is causal in nature. One should be aware, however, that the same bias (i.e., systematic error) could exist in multiple studies and produce an apparent artifactual consistency (Mausner et al. 1974).

The use of renal dialysis patients as a study population entails an increased danger of having a systematic error producing a spurious association. ESRD patients suffer from a number of systemic pathologies and are exposed to a great number of agents in the course of their treatment. Therefore, when examining causal associations in this group, it is necessary to be sure the cause is not attributable to the effect of some unadjusted factor.

The bias described here is called indirect association. Indirect association in a renal dialysis population could be the effect of a factor or factors, other than the one identified, which cause the determined effect. For example, in attempting to identify DEHP as a cause of cancer in ESRD patients, the investigator must rigorously adjust for a multitude of pathologic and iatrogenic variables other than this plasticizer before the causal link can be substantiated.

Strength of Association refers to the ratio of disease rates for those with and without the hypothesized factor. The likelihood of a causal relation is strengthened if a dose-response effect (gradient) can be demonstrated. Thus, with increasing levels of exposure to the factor, a corresponding rise in the occurrence of the disease is found (Mausner et al. 1974).

Renal dialysis patients utilize three different treatment modalities, each of which exposes the individual to a complex of agents. In addition to dialysis, the ESRD population receives a high number of blood infusions and medications. The main source of contamination from DEHP, other than dialysis, comes from blood stored in PVC blood bags. Therefore, all three dialysis patient groups--hemo, peritoneal, and continuous ambulatory peritoneal--are exposed to the agent DEHP.

As a patient's condition declines, a greater number of dialysis treatments may be needed and a greater number of transfusions are likely to be required. This factor makes it difficult to determine if the development of a condition such as cancer is more evident in more severe ESRD patients, or is caused by exposure to the plasticizer.

Specificity of Association measures the degree to which one particular exposure produces one specific disease (Mausner et al. 1974). ESRD patients are exposed to a great number of potentially toxic agents, each of which has a determined singular potential effect as well as many undetermined effects.

In addition, ESRD patients exhibit a large range of pathologies which vary with the nature of the underlying disease entity. Due to the multiple factors associated with the ESRD patients, it is difficult--if not impossible--to determine which of these factors is the sole preceding agent responsible for the manifestation of an outcome such as cancer.

Temporal Relationship of Association requires that exposure to the putative factor must antedate the onset of disease, and must allow for any necessary period of induction and latency (Mausner et al. 1974). The disease process which brought about chronic renal failure will antedate the exposure to any treatment agent to which the individual is exposed, and may itself influence the onset of cancer.

Without a successful transplantation intervention, the end stage renal disease patient has a seven- to ten-year maximum life expectancy after the onset of chronic renal failure. This period is too short a timeframe to expose and induce the development of a chronic disease such as cancer. Consequently, the patient may not live long enough to develop the specific disease.

Coherence of Association infers biological plausibility, which may have been established in animal models (Mausner *et al*. 1974).

There are a great many difficulties associated with the extrapolation of animal data to human populations, in general. This situation is further complicated by consideration of a severely ill study population, such as patients suffering from chronic renal failure. The metabolism of substances such as DEHP in ESRD patients differs from that in healthy individuals. In healthy individuals, most of the DEHP is excreted within 24 hours. Renal dialysis patients cannot excrete, and store this substance in their tissues.

Studies to date have not used animals with chronic renal failure over a large enough time frame to make them even somewhat comparable to ESRD patients.

5.2 Analytic Approaches

Since chronic diseases develop over a prolonged time interval, the etiologic study of their conditions requires an analysis of the events which occur during this time. For ESRD patients, such analysis must include the problems of confounding factors associated with the various treatment modalities for end stage renal disease. The following paragraphs examine these problems from a statistical standpoint. Each factor and its potentiality as a cause of cancer is presented through a discussion of each issue, its effect and the problems associated with correcting for it.

5.2.1 Multiple Causal Paths

Figure 5-1 presents a flow chart of potential development of cancer in an ESRD patient in which the broken lines represent paths which may lead to a particular treatment and the solid lines indicate probable physical results. The possible interrelationships between renal disease and associated treatment therapies, and the likelihood of additional diseases, are presented in a simplified manner, but are sufficient to illustrate the critical confounding of factors which could be responsible for primary liver cancer or other types of malignancy.

It has been suggested that the sensitivity of ESRD patients to primary liver cancer or other cancer would be advantageous in determining efficiently, with respect to time and sample size required, the development of these diseases in a study population. However, the case is not simply that these patients are more sensitive to malignancy in the way that mice are bred to be, but that they are subject to several causative factors which can lead to cancer by interconnected etiological paths. Discrimination among these factors would be almost impossible, particularly in a retrospective study. As shown in figure 5-1, the renal disease process itself, through attendant uremia and protein-calorie malnutrition, leads to immunosuppression and hence to increased cancer risk. In addition, the treatment therapies include transplantation, which involves immunosuppressive therapy both before surgery and after (frequently for an indefinite period). Thus, multiple routes emanate from both the disease process and the treatment to immunosuppression, which in turn increases the risk of malignancies of all types.

Treatment combinations of nephrectomy, transplantation, and blood transfusions increase the incidence of hepatitis B, which is a risk factor in hepatic cancer. At the same time, the treatment process of hemodialysis itself also increases the risk of hepatitis B and, hence, of hepatic cancer.

5.2.2 Indiscriminate Exposure Measure

An even more difficult, in fact prohibitive, problem involved in differentiating among the causative factors is the acute exposure during dialysis

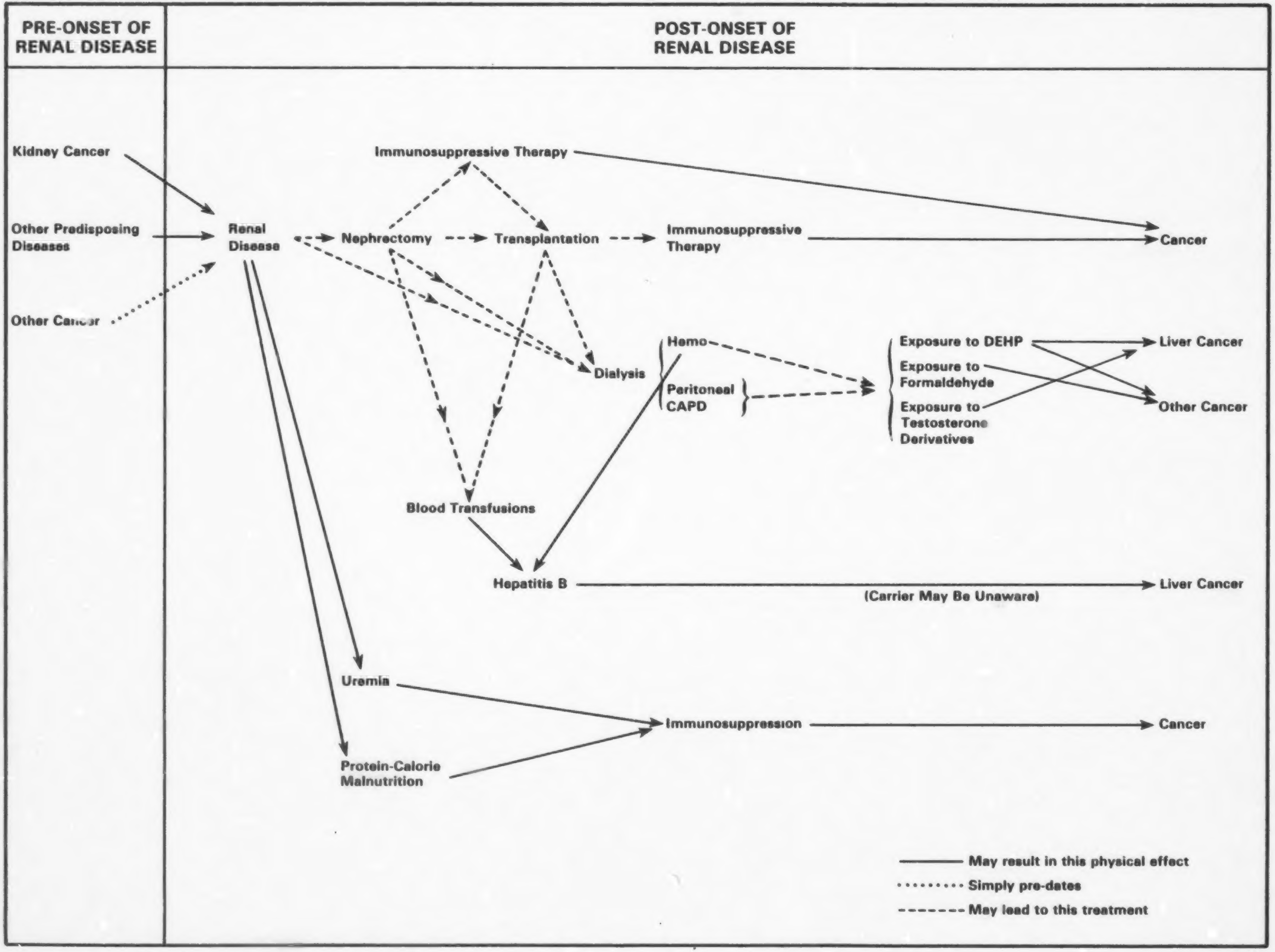

PRE-ONSET OF RENAL DISEASE
POST-ONSET OF RENAL DISEASE
Kidney Cancer
Other Predisposing Diseases
Other Cancer
Renal Disease
Immunosuppressive Therapy
Nephrectomy
Transplantation
Immunosuppressive Therapy
Cancer
Dialysis
Hemo
Peritoneal CAPD
Exposure to DEHP
Exposure to Formaldehyde
Exposure to Testosterone Derivatives
Liver Cancer
Other Cancer
Blood Transfusions
Hepatitis B
Liver Cancer
(Carrier May Be Unaware)
Uremia
Protein-Calorie Malnutrition
Immunosuppression
Cancer
May result in this physical effect
Simply pre-dates
May lead to this treatment

Figure 5-1. POSSIBLE INTERRELATIONS BETWEEN CANCER (LIVER AND OTHER), RENAL DISEASE AND ITS TREATMENT

simultaneously to several known or potential carcinogenic agents: to DEHP through the PVC-tubing; to formaldehyde through sterilizing agents; to zinc/cadmium contaminants through membranes; to testosterone derivatives which are specific for hepatic cancer; to direct entry into the blood stream of fluoride, chloramine, nitrate-nitrite, aluminum, and other trace metals in the water (Kjellstrand 1978); and to complement activation from membranes which produces the immunosuppressant state of leukopenia (Shin 1978). Moreover, other confounding exposures undoubtedly occur in the dialysis process with effects which are as yet undiscovered.

Thus, the measure proposed to determine the exposure to DEHP of ESRD patients--duration on dialysis--is simultaneously the surrogate measure for several other possible carcinogenic factors, as shown in table 5-1. Even the specific cancer of interest, primary liver cancer, can result from at least three factors: 1) DEHP and testosterone derivatives, whose individual measures are identically determined by duration of any type of dialysis; 2)hepatitis B, whose incidence is closely related to the duration of hemodialysis by the process itself; and 3) the duration itself of any type of dialysis because of its positive correlation with the number of blood transfusions and, hence, with the risk of hepatitis.

It is not possible, as had been proposed, to use patients on peritoneal dialysis as a control group vis-a-vis those on hemodialysis in order to represent differentiation of degree of exposure to DEHP, since there is actually very little exposure difference between them. Peritoneal dialysis involves exposures of 3 to 5 mg, while hemodialysis involves exposures of 4 to 8 mg. (Harris 1981). Thus, no method presents itself by which an end result such as hepatic or other cancer could be traced specifically to exposure to DEHP in ESRD patients.

5.2.3 Dominating Competitive Risks

Although several factors related to the disease process and to its treatment could lead to an increased risk of cancer in ESRD patients, their extremely high risk of death from vascular diseases and from infectious

TABLE 5-1. FACTORS FOR WHICH DIALYSIS DURATION IS AN IDENTICAL, SURROGATE MEASURE

The duration on dialysis is an identical surrogate measure of the exposure to the following potential etiologic factors in the development of cancer:

1. Exposure related to the dialysis treatment process itself:
    a. DEHP
    b. Formaldehyde
    c. Testosterone derivatives
    d. Zinc/cadmium contaminates

2. Exposure directly reflecting the passage of time:
    a. Factors due to the duration and progression of renal disease:
        - Immunosuppressive effects of uremia
        - Immunosuppressive effects of protein-calorie malnutrition
        - Increased risk of hepatitis due to additional blood transfusions
    b. Factors due to the duration of post-transplantation therapy:
        - Immunosuppression
    c. Factor due to aging:
        - Increased risk of malignancy.

diseases dominates their mortality model, and would reduce drastically the probability of observing cancer development in them.

In a study of causes of mortality in a single year among patients on dialysis (Moorhead 1973), 50.5 percent of the deaths were due to vascular disease, 19.4 percent to infectious disease, and only 2.0 percent to malignant disease. Clearly, intervention by deaths from more immediate risks would severely censor the observation of cancer deaths, particularly of relatively infrequent liver cancer deaths, in this patient population. Moreover, statistical adjustment for competitive risks so disproportionately greater than the mortality risk of interest could obscure the estimate of the latter's probability of occurrence.

5.2.4 Size of Study Population

As with any study using a selected population, consideration must be given to size of the group to be observed in order to determine the study method to be used. Two of the more common study methods in this area are cohort and case-control.

Cohort Study

The 1970 annual incidence of neoplasia for the 45 to 70 year age group in the U.S. was approximately 623 per 100,000. If the asbestos model is the appropriate one, then a five-fold increase in incidence is the largest that would be expected in the exposed population. The sample size required to detect a significant increase (one-tailed test) over the control group with a type I error of .05 and power of .90 (Snedecor and Cochran 1967) would be approximately 500 person-years. However, if just a doubling of the incidence could be expected, then a sample of 4,100 would be needed; and if only a 50 percent increase in cancer occurred, it would require a sample of 13,650 to detect the difference.

The incidence of primary liver cancer in the U.S. population is less than three per 100,000, and therefore much larger sample sizes are needed to detect significant differences when the actual elevation of risk is of the orders cited above. For example, if a five-fold increase in risk existed in the study population, 107,500 person-years would be required to detect it with the significance level and power stated above. If the increased risk of primary liver cancer were less than five-fold, for example two-fold, the required sample size would be 860,000 person-years.

Moreover, these sample sizes are only for a simple one-tailed test of difference between proportions or incidence without the classification which would be necessary for factor-adjustment, which would increase the sample size required.

Case-Control Study

Case-control studies with measured exposure are more statistically sensitive (powerful) than cohort analysis and thus do not require sample sizes as large for the same detection level. However, in these data, differences in DEHP exposure between cases and controls would be indeterminate, since the only measure available--time on dialysis--measures the potential of multiple factors indiscriminately.

It is possible that an epidemiologic study protocol could be developed that would address successfully some segment of the end stage renal disease patient population, relying on rigorous segregation of comparable elements of the study population and adequate attention to the multitude of confounding factors. However, it is unlikely, given the chronic illness of the patient population and the limited prognosis for survival, that such an epidemiologic study would succeed in determining either association or causality of so subtle a contaminant as DEHP relative to cancer mortality in the population.

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